# COMPARISON OF OAEs SCREENING AND CLINICAL AUDIOMETRY IN DIABETIC PATIENTS WITHOUT HEARING SYMPTOM

**WEERAYA CHARLEE**

**A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF SCIENCE (COMMUNICATION DISORDERS) FACULTY OF GRADUATE STUDIES MAHIDOL UNIVERSITY 2015**

**COPYRIGHT OF MAHIDOL UNIVERSITY**

Thesis
entitled

# COMPARISON OF OAEs SCREENING AND CLINICAL AUDIOMETRY IN DIABETIC PATIENTS WITHOUT HEARING SYMPTOM

..………………….…………..….……..………
Miss.Weeraya Charlee
Candidate

..………………….…………..….……..………
Assoc. Prof. Krisna Lertsukprasert,
M.A. (Communication Disorders)
Major advisor

..………………….…………..….……..………
Prof. Chatchalit Rattarasarn,
M.D. (Endocrinology and Metabolism)
Co-advisor

..………………….…………..….……..………
Lect. Sakda Arj-ong Vallipakorn,
M.D., Ph.D. (Clinical Epidemiology)
Co-advisor

………………….…………..….……..………
Prof. Patcharee Lertrit,
M.D., Ph.D. (Biochemistry)
Dean
Faculty of Graduate Studies
Mahidol University

..………………….…………..….……..………
Assoc. Prof. Krisna Lertsukprasert,
M.A. (Communication Disorders)
Program Director
Master of Science Program in
Communication Disorders
Faculty of Medicine
Ramathibodi Hospital
Mahidol University

Thesis
entitled
**COMPARISON OF OAEs SCREENING AND CLINICAL AUDIOMETRY IN DIABETIC PATIENTS WITHOUT HEARING SYMPTOM**

was submitted to the Faculty of Graduate Studies, Mahidol University
for the degree of Master of Science (Communication Disorders)
on
May 22, 2015

……………………………...………
Miss.Weeraya Charlee
Candidate

…………………..…..……………...…
Maj.Gen.Assoc.Prof. Pongthep Harnchumpol,
M.A. (Communication Disorders)
Chair

……………..…………..……..………
Assoc.Prof. Krisna Lertsukprasert,
M.A. (Communication Disorders)
Member

……………………………………….
Lect. Sakda Arj-ong Vallipakorn,
M.D., Ph.D. (Clinical Epidemiology)
Member

…..…..…..……………..………..……...…
Prof. Chatchalit Rattarasarn,
M.D. (Endocrinology and Metabolism)
Member

……………………...…...………….
Prof. Patcharee Lertrit,
M.D., Ph.D. (Biochemistry)
Dean
Faculty of Graduate Studies

……………………...…..………...….
Prof. Winit Phuapradit,
M.D., M.P.H. (Maternal and Child Health)
Dean
Faculty of Medicine
Ramathibodi Hospital
Mahidol University

# ACKNOWLEDGEMENTS

I would like to gratefully and sincerely thank Assoc. Prof. Krisna Lertsukprasert, my advisor for her guidance, inspiration, and support during my research. Her suggestions have been precious for the development of all thesis content and make this thesis complete success.

I would like to thank Prof. Chatchalit Rattarasarn, my co-advisor for his helpful comments, furthermore, he gave me an opportunity to collect patients data at out-patient endocrine clinic at Ramathibodi hospital, so this made the process of thesis easier. Special thanks to volunteers who attended in this research. I was very appreciate their coordination and sacrifice until the progress was finished.

I would like to thank Lect. Sakda Arj-ong Vallipakorn, my co-advisor for his assistance in statistical analysis of the data. His experience and intelligence can manage data perfectly.

I would like to thank graduate alumni association of Mahidol University for granting the thesis partially support scholarship for academic year 2014.

I am particularly indebted to my family, friends and colleagues for their help, support and encouraging me to pass all obstacles during this thesis.

Weeraya Charlee

COMPARISON OF OAEs SCREENING AND CLINICAL AUDIOMETRY IN DIABETIC PATIENTS WITHOUT HEARING SYMPTOM

WEERAYA CHARLEE 5537600 RACD/M

M.S. (COMMUNICATION DISORDERS)

THESIS ADVISORY COMMITTEE : KRISNA LERTSUKPRASERT, M.A., CHATCHALIT RATTARASARN, M.D., SAKDA ARJ-ONG VALLIPAKORN, M.D., Ph.D.

ABSTRACT

The main objectives of this study was to evaluate the efficiency of otoacoustic emission (OAE) screening for both transient evoked otoacoustic emissions (TEOAEs) and distortion product otoacoustic emissions (DPOAEs) and to assess the hearing screening, compared with clinical audiometry in 142 diabetic patients without hearing symptoms (71 females and 71 males, aged 30-60 years old), who visited the out-patient endocrine clinic at Ramathibodi Hospital, Bangkok. They were not suspected to have outer and/or middle ear problems. The general information and medical history of all subjects were collected before the OAE screening and clinical audiometry tests. All data were analyzed using STATA 13.0 software (College Station, TX, USA). The results showed that the sensitivity of TEOAEs was 27% and 29%, while the specificity was 96% and 92% in right and left ears, respectively. The accuracy was 50% and 69%, positive predictive value (PPV) was 93% and 87% in right and left ears, respectively, and negative predictive value (NPV) was 40% in both ears. The positive likelihood ratio (LR+) was 6.85 and 3.63, and negative likelihood ratio (LR-) was 0.75 and 0.77 in right and left ears, respectively. The sensitivity of DPOAEs was 66% and 69%, and its specificity was 89% and 83% in right and left ears, respectively, with an accuracy of 74% in both ears. The PPV was 93% and 89%, NPV was 57% and 58%, LR+ was 6.00 and 4.06, and LR- was 0.38 and 0.37 in right and left ears, respectively. In summary, the DPOAEs were more efficient for the detection of hearing impairment in diabetic patients than TEOAEs. Moreover, the test was simple, fast, and costs less, and could be used by non-professional personnel.

KEY WORDS: OAEs SCREENING / CLINICAL AUDIOMETRY / DIABETES MELLITUS

84 pages

การศึกษาเปรียบเทียบการตรวจคัดกรองการได้ยินและการตรวจการได้ยินในผู้ป่วยเบาหวานที่ไม่แสดงอาการด้านการได้ยิน COMPARISON OF OAEs SCREENING AND CLINICAL AUDIOMETRY IN DIABETIC PATIENTS WITHOUT HEARING SYMPTOM

วีรญา ชาลี 5537600 RACD/M

วท.ม. (ความผิดปกติของการสื่อความหมาย)

คณะกรรมการที่ปรึกษาวิทยานิพนธ์ : กฤษณา เลิศสุขประเสริฐ, M.A., ชัชลิต รัตรสาร, M.D., ศักดา อาจองค์ วัลลิภากร, M.D., Ph.D.

บทคัดย่อ

วัตถุประสงค์หลักของการศึกษาในครั้งนี้เพื่อประเมินประสิทธิภาพของเครื่องมือคัดกรองการได้ยินทั้ง transient evoked otoacoustic emissions (TEOAEs) และ distortion product otoacoustic emissions (DPOAEs) ในการช่วยตรวจพบปัญหาด้านการได้ยินโดยเปรียบเทียบกับผลตรวจการได้ยินทางคลินิก ในผู้ป่วยเบาหวานที่ไม่แสดงอาการด้านการได้ยิน จำนวน 142 คน (หญิง 71 คน, ชาย 71 คน,อายุระหว่าง 30-60 ปี) ที่มารับการรักษาที่คลินิกโรคเบาหวาน โรงพยาบาลรามาธิบดี กรุงเทพมหานคร และไม่มีสิ่งที่แสดงว่าอาจมีความผิดปกติของหูชั้นนอกและ/หรือหูชั้นกลาง ในการศึกษาครั้งนี้ผู้เข้าร่วมวิจัยจะต้องตอบแบบสอบถามข้อมูลทั่วไปและประวัติการรักษา ก่อนที่จะได้รับการตรวจคัดกรองการได้ยินและตรวจการได้ยินทางคลินิก การวิเคราะห์ข้อมูลใช้โปรแกรมคอมพิวเตอร์สำเร็จรูป STATA 13.0 software (College Station, TX, USA) ผลการศึกษาพบว่า TEOAEs มีความไวในการตรวจพบปัญหาด้านการได้ยินในหูขวาและหูซ้ายร้อยละ 27,29 มีความจำเพาะร้อยละ 96,92 มีความความแม่นยำร้อยละ50,69 มีค่าพยากรณ์บวกร้อยละ93,87 มีค่าพยากรณ์ลบร้อยละ 40 ในหูทั้งสองข้าง มีค่า Positive likelihood ratio 6.85,3.63 และค่า Negative likelihood ratio 0.75,0.77 ในหูขวาและหูซ้ายตามลำดับในขณะที่ DPOAEs มีความไวร้อยละ 66,69 มีความจำเพาะร้อยละ 89,83 ในหูขวาและหูซ้ายตามลำดับ มีความความแม่นยำร้อยละ74 ในหูทั้งสองข้าง มีค่าพยากรณ์บวกร้อยละ93,89 มีค่าพยากรณ์ลบร้อยละ 57,58 มีค่า Positive likelihood ratio 6.00,4.06 และค่า Negative likelihood ratio 0.38, 0.37ในหูขวาและหูซ้ายตามลำดับ จากผลการศึกษาครั้งนี้แสดงให้เห็นว่า DPOAEs เป็นการตรวจคัดกรองการได้ยินมีประสิทธิภาพในการช่วยตรวจพบปัญหาด้านการได้ยินในผู้ป่วยเบาหวานดีกว่า TEOAEs และยังเป็นการตรวจที่ทำได้ง่าย ใช้เวลาน้อย ราคาไม่แพง และไม่จำเป็นต้องอาศัยบุคลากรที่มีความรู้เฉพาะด้านในการตรวจคัดกรอง

84 หน้า

# CONTENTS

# CONTENTS (cont.)

# LIST OF TABLES

# CHAPTER I
# INTRODUCTION

## 1.1 Background and significance

Hearing loss is one of the health issues experienced by an individual with diabetes. In recent years, there were reports showing 73% of diabetic patients experiencing the hearing loss (1). Sensorineural hearing loss is the most common form of diabetes-inducing hearing loss. It involves the loss in the intensity or loudness, frequency resolution, dynamic range, and temporal resolution. Unfortunately, both patients and their families do not aware about hearing problem. Because the diabetes-related hearing loss has been described as bilateral; slowly progressive sensorineural impairment with gradual onset, therefore they will know the problem once their hearing loss is severe, and harms their listening ability and communication in daily life. Depending on the degree of hearing loss, the patients may still be able to hear but may have the difficulties to understand whisper, speech on television, phone conversation, and communication in noisy situations. Moreover, they may have the difficulties to identify the sound and location in an environment, or hardly hear the high frequency speech sounds such as the fricatives “s”, “f” or “th”. Most of the problems focus on the inability to understand speeches, rather than a loss in loudness perception (2).

Ignorance to the hearing loss problem and lack of awareness in the negative consequences of hearing loss result in the auditory deprivation condition, then the afterward management is failed to succeed. Therefore, the appropriate medical care and treatment are necessary for the diabetic patients in order to have an early detection of hearing loss problem and prevent the negative outcomes such as the poor quality of life, loneliness, social isolation, low self-esteem, insecurity, frustration, poor personal and family relationships, decrease in cognitive skills, unemployment, lower earning power and early retirement.

Diabetes mellitus is a chronic disease threatening to Thai people for a long time. At this moment, the proportion of patients with diabetes is slightly increased because of their habits; for example, an inappropriate eating without daily exercise. Interestingly, the late diagnosis causes the delay of blood glucose control including, hypertension and hyperlipidemia due to the fact that diabetes prevalence is gradually happened. It is rather difficult to predict the prognosis (3).

A survey of Thai people's health during 2008-2009 found that they had been facing the diabetes problem. Diabetes was found up to 6.9 % in the people older than 15 years old (7.7 % in females and 6% in males), and there were 10.7 % with pre-diabetes (9.5 % in females and 11.8% in males) (3).

In Thailand, there were few studies focusing on the connection between hearing loss and diabetes mellitus. Ruencharoen studied the audiological findings in diabetic patients with and without hearing symptom. The results showed that the hearing impairment in diabetic patients was more severe than the control subjects. Although, the hearing impairment in symptomatic diabetic patients was similar to those in asymptomatic patients, the subclinical involvements were more severe (4). This study demonstrated that the hearing loss apparently appeared in the asymptomatic diabetic patients.

Diabetes is associated with various health complications, particularly in vascular and neuropathic conditions of eyes, kidneys and heart (3). However, diabetes may also lead to other important consequences. It has been demonstrated high prevalence of hearing impairment in diabetic patients (1). Recent evidence confirms the link between diabetes and hearing loss. Bainbridge et al. studied the prevalence of hearing loss in 5,140 individuals during 1999 to 2004. The results showed that the prevalence of hearing loss was more than double for those with diabetes, compared to those without diabetes. Moreover the persons with diabetes had higher thresholds at all frequencies more than those without diabetes, and this difference seemed to widen at the frequencies greater than 2000 Hz. In particular, the hearing loss in the low or mid frequency sounds was 21% in diabetic participants, compared with 9% in those without diabetes. Diabetes and hearing loss was strongly related in the high frequency range. The high frequency hearing loss was found in 54% of individuals with diabetes versus 32% of individuals without diabetes. The study also found that the adults with pre-diabetes, whose blood glucose is higher than normal but not high enough for a diabetes diagnosis, had higher rate of hearing loss at 30%, compared to those with normal blood glucose levels (5).

Type 2 diabetes and hearing loss are usually associated with age. The hearing loss is highly prevalent and more severe among the old people with diabetes. In other words, the age is a risk factor that induces the hearing loss. However there are some researches, suggesting that children with type 1 diabetes are also likely to face the hearing loss (5). Cheng et al. (6) found that in 63 diabetic children, less than 18 years of age, had lower hearing ability than 63 non-diabetic control subjects. The greatest hearing difference was found in the mid to high frequencies. The incidence and severity of hearing loss seemed to be relative to how long the children had the diabetes and how well their glucose levels were controlled. It proves that the hearing loss may be an under-recognized complication in both type 1 and type 2 diabetes.

The underlying mechanisms of diabetes-inducing hearing loss, are not fully understood. There are several ways that the diabetes can affect a person's hearing ability. Some biological mechanisms might explain the association between diabetes and hearing loss. The well-established complications of diabetes involve the pathogenic changes to the microvasculature and sensory nerves (7). The postmortem observations of diabetic patients show the thickening of capillaries in the stria vascularis (8); the thickened walls of basilar membrane's vessel and greater loss of outer hair cells in the lower basal turn (9), and demyelination of the eighth cranial nerve, which help the transmission of auditory signals from the cochlea to the brainstem (10). The narrowing of the internal auditory artery is another vascular change caused by the diabetes (11). Hearing function also depends on the small blood vessels and nerves. These organs, including function of inner ear around the basal turn of cochlea which respond to the sound of high frequencies, are abnormal in diabetes (3). Some patients may still hear well, according to their answers in the questionnaire. Using the questionnaire to survey patients' hearing problem is convenient, but the results from the questionnaire may not be accurate. It is better to provide the hearing screening to detect the hearing problem earlier (12).

Clinical audiometry is the gold standard of hearing test. It is the test for diagnosis of hearing loss. Various audiometric tests determine the lowest intensity of sound, which an individual can perceive auditory stimuli (hearing threshold) and distinguish the different speech sounds.  It indicates that the hearing loss is caused by an outer ear, a middle ear, an inner ear, or an acoustic nerve problem. This test is usually administered by an audiologist.

Currently, there are many advanced hearing technologies for using in the audiology clinics, such as the transient evoked otoacoustic emissions (TEOAEs) and distortion product otoacoustic emissions (DPOAEs) which can be used conveniently and easily as screening test by non-professional personnel. TEOAEs and DPOAEs are the objective evidences of the cochlear function (cochlea's outer hair cells). TEOAEs respond to a series of transient stimuli, wideband clicks, or chirps (frequencies between 2000 and 4000 Hz.), and DPOAEs respond to a pair of pure tones at frequencies f1 and f2. A series of stimuli is sent into the ear canal and then stimulate the cochlea. The result of otoacoustic emissions (OAEs) comes from the inner ear through the middle ear. The responses are recorded by a very sensitive microphone in the ear canal during the stimulus presentations.

The hearing loss could be detected as early as possible with simple technique and less time consumption. It is important that the physicians encourage diabetic patients to get their hearing test regularly. If the hearing loss is identified, a management should be provided appropriately.

The aim of this study is to compare the relationship between hearing screening test and clinical audiological test in diabetic patients who are not concerned about the hearing symptom in endocrine clinic. The study should support the development of a guideline for hearing loss detection in diabetic patients.

## 1.2 Statement of the problem

The hearing loss is a health complication of diabetes, representing one of the most common consequences of the disease. With studies indicating that the prevalence of hearing loss is more than double for those people with diabetes, compared to those without, it is important to include hearing assessment to be a part of diabetes’s health check. The clinical audiometry testing is used by an audiologist to identify and diagnose the hearing loss, while OAEs is a screening test, which can be performed by non-professional personnel and takes only 1-2 minutes without need of patient co-operation.

The objective of this study is to compare the relationship between hearing screening test and clinical audiometry test. The test includes TEOAEs, DPOAEs, and clinical audiometry testing, then examines the sensitivity and specificity of OAEs device measurement comparing to the outcome of clinical audiometry.

## 1.3 Purposes of the study

1.3.1 Evaluate of the efficiency of OAEs screening, compared with clinical audiometry in diabetic patients without hearing symptom.

1.3.2 Comparison of TEOAEs results and clinical audiometry.

1.3.3 Comparison of DPOAEs results and clinical audiometry.

## 1.4 Research question

1.4.1 What is the prevalence of hearing loss in diabetic patients?

1.4.2 Is there any correlation between TEOAEs and clinical audiometry?

1.4.3 Is there any correlation between DPOAEs and clinical audiometry?

1.4.4 Are the screening results of TEOAEs different from DPOAEs' results?

## 1.5 Hypothesis

1.5.1 Diabetic patients without hearing symptom have hearing loss at some degree.

1.5.2 TEOAEs screening results correlate to clinical audiometry.

1.5.3 DPOAEs screening results correlate to clinical audiometry.

1.5.4 TEOAEs screening results correlate to DPOAEs.

## 1.6 Expected benefits and application

1.6.1 Early diagnose the hearing loss in diabetic patients without hearing symptom.

1.6.2 Ensure the efficiency of the OAEs device as the hearing screening tests.

1.6.3 Help the health personnel and clinician to realize the importance of hearing impairment in diabetic patients.

1.6.4 Diabetic patients with hearing loss will get a proper management.

# CHAPTER II
# LITERATURE REVIEW

## 2.1 Diabetes mellitus

Diabetes mellitus is a metabolic disease in which the blood glucose levels are high over a prolonged term, either because the pancreas cannot produce enough insulin, resulting in the inadequate insulin production, or the body's cells cannot respond properly to the insulin production, or both. The prevalence of diabetes is swiftly increasing worldwide and the World Health Organization has prognosticated that in 2030 the number of adults with diabetes will almost double, from 177 million in 2000 to 370 million, worldwide (13).

### 2.1.1 Diagnosis of diabetes mellitus

Diagnosis of diabetes mellitus is based on classical symptoms (such as polyuria, weight loss, thirst, fatigue, and muscular weakness) and high plasma glucose levels. The criteria for diagnosis of diabetes mellitus are as follows (14):

1. Patients, who have obvious diabetic symptoms such as unexplained weight loss, increased thirst, excessive urination, can test the plasma glucose any time without fasting. If the results show plasma glucose ≥ 200 mg/dL (11.1 mmol/l), they will be diagnosed as diabetes.

2. After fasting at least 8 hours, a person can test the fasting plasma glucose (FPG) in the morning. If the results show FPG ≥ 126 mg/dL (7.0 mmol/l), they will be diagnosed as diabetes.

3. Oral glucose tolerance test (OGTT) will be diagnosed as diabetes, if plasma glucose levels at 2 hours after taking 75 grams glucose is ≥ 200 mg/dL (11.1 mmol/l).

4. HbA1c between 6.0-6.4% indicates the risk of diabetes around 25-50% and diabetic patients will have HbA1c ≥ 6.5%. However, this test is not popular

because Thailand cannot control the standardization and quality in laboratory. Importantly, the cost of test is more expensive than plasma glucose test (15).

### 2.1.2 Classification of diabetes mellitus

The majority of diabetic cases fall into two categories, namely type 1 and type 2 diabetes (16,17,18).

#### 2.1.2.1 Type 1 diabetes

Type 1 diabetes, also called juvenile onset diabetes or insulin dependent diabetes mellitus, is an insulin insufficiency syndrome caused by beta cells (β cells) in pancreas destruction. The type 1 diabetes represents around 5-10% of all diabetes' cases, and is customarily diagnosed in childhood (majority at the age of 4 to 5 years), or teens and early adult lives; although, it can be experienced at any ages (19,20).

#### 2.1.2.2 Type 2 diabetes

Type 2 diabetes, also called non-insulin dependent diabetes mellitus, is caused by the declined sensitivity of target tissues towards insulin or insulin resistance (21). It can induce the cells of body not to respond properly to the insulin production (22).

This type of diabetes is the major form of diabetes, which mostly found around 90-95% of all cases (23). The incidence of type 2 diabetes increases by age, and most cases are diagnosed after 40 years of age (24). Many people with type 2 diabetes do not realize that they have the disease, which can lead to long-term health complications.

#### Other categories of diabetes

Other categories of diabetes are comprised of gestational diabetes and other rare causes.

The gestational diabetes (a state of hyperglycemia which develops during pregnancy) appears in a pregnant woman who never have the diabetes before, and it is often diagnosed in the middle or late pregnancy during routine blood screening. There is no specific cause but it is believed that the hormones produced during pregnancy increase the insulin resistance, resulting in the impaired glucose tolerance.

Other rare causes of diabetes are genetic syndromes, certain surgeries and medications, diseases such as cystic fibrosis, acquired processes such as pancreatitis, viruses, exposure to certain drugs, infections, and unknown causes. These types of diabetes are found only about 1-5% of all diabetes cases (17,18).

### 2.1.3 Pathophysiology of diabetes mellitus

#### 2.1.3.1 Type 1 diabetes

Type 1 diabetes is a chronic autoimmune disorder, associated with selective annihilation of insulin-producing pancreatic beta cells. The autoimmune annihilation of pancreatic beta cells induces an insufficiency of insulin secretion. Then the loss of insulin secretion leads to the increase of glucagon secretion from the pancreatic alpha cell ($\alpha$-cells), which results in the metabolic derangements connected with the type 1 diabetes. The rate of beta cells destruction is quite variable. It is rather quick in infants and children, but slow in adults.

Moreover, the type 1 diabetes can occur in the absence of autoimmune antibody and without evidence of any autoimmune disorder. It is a progressive disease with marked hyperglycemia condition (25-27).

#### 2.1.3.2 Type 2 diabetes

Type 2 diabetes is a heterogenous disorder caused by a combination of genetic factors, associated with the impaired insulin secretion, insulin resistance, and environmental factors. The type 2 diabetes has the genetic association greater than type 1 diabetes. Its pathophysiology may range from a predominantly insulin resistance with relative insulin deficiency or a predominantly insulin secretory defect with insulin resistance.

The environmental factors such as obesity, lack of exercise, over eating, excessive body weight, insufficient energy consumption, alcohol, smoking, stress, as well as aging are the independent risk factors of type 2 diabetes. The obesity caused by deficiency of exercise accompanies with a decline in muscle mass and increase of insulin resistance. The prevalence of type 2 diabetes is increasing in those with obesity.

Most patients with type 2 diabetes are not diagnosed early because the symptoms of disease develop gradually, and it is not severe enough to produce the classical symptoms of diabetes in the initial stages. Therefore, these patients are at higher risk to develop diabetic complications (27-29).

### 2.1.4 Complications of diabetes mellitus

Diabetes mellitus can influence every human system, such as cardiovascular, vision, kidney, skin, auditory, and etc. The unawareness of patients may directly affect diabetes mellitus' complications. The lifestyle, aging, and uncontrolled blood glucose levels are common causes for these complications. The complications of diabetes mellitus can be divided into two groups as acute (short term) and chronic (long term) complications.

#### 2.1.4.1 Acute complications

Acute complications can suddenly and severely occur at any time. It is not depended on the duration of disease, so the complications are likely to cause the metabolic problems. Most of acute complications are about blood glucose derangement; for example, diabetic ketoacidosis, hyperglycemic hyperosmolar state, and hypoglycemia.

**a. Diabetic ketoacidosis**

Diabetic ketoacidosis (DKA) is an acute and dangerous complication caused by the inadequate insulin administration. It is considered as a medical emergency with a mortality rate approximately at 5%. DKA is occurred by severe insulin insufficiency and this leads to the hyperglycemia, dehydration, production of ketone bodies, and acidosis. The DKA is defined as the presence of hyperglycemia (glucose > 250 mg/dL), ketosis, and acidemia (pH < 7.3) (30). It commonly develops in a short period (usually less than 24 hours).

However, there are about 20% of patients newly diagnosed as type 1 diabetes with DKA and some as type 2 diabetes with DKA. DKA can be the first manifestation of type 1 diabetes in a previously undiagnosed patient or can occur in a patient with type 1 diabetes whose insulin requirements arise during the medical stress. It can also occur in patients with type 2 diabetes who have a predominant insulin secretory defect during the severe medical stress.

Clinical symptoms of DKA consist of the history of abdominal pain, polyuria, nausea, vomiting, fatigue, polydipsia, drowsiness, lethargy, deep and rapid breath, increased thirst, dehydration, and fruity-smelling breath. Some patients may have symptoms of an underlying infection, such as urinary tract infection, pneumonia or gastroenteritis (31).

**b. Hyperglycemic hyperosmolar state (HHS)**

HHS is the medical term characterized by severe hyperglycemia and hyperosmolarity. This condition represents the metabolic derangements, and it occurs when the insulin insufficiency (relative to insulin requirements) leads to hyperglycemia, which contributes to dehydration, and finally results in a severe hyperosmolar state. The basic pathophysiology of HHS is similar to that of DKA (32). The precipitating causes of HHS are comprised of cerebrovascular accidents, pancreatitis, myocardial infarction, and alcohol abuse. The majority of diabetic patients with HHS have the plasma glucose levels > 600 mg/dL, while some patients may have lower plasma glucose levels at the time of presentation.

Clinical symptoms of HHS consist of weight loss, increasing polyuria, polydipsia, malaise, nausea, vomiting, and dehydration. Diabetic patients with HHS tend to be more dehydrated at the time of presentation than the patients with DKA (28-30).

**c. Hypoglycemia**

Hypoglycemia is a condition characterized by the abnormal low blood glucose levels (commonly less than 70 mg/dL or 3.9 mmol/L), which may be also referred as an insulin reaction, or insulin shock. This condition has many causes but it is almost invariably an adverse effect of therapy in diabetes (31). The principal factors, associated with hypoglycemia in diabetes, are the excessive dose of insulin, deficient or delayed ingestion of food, and sudden exercise.

Clinical symptoms of hypoglycemia are varied such as confusion, dizziness, rapid heartbeat, shakiness, hunger, headaches, irritability, racing pulse, pale skin, sweat, trembling, weakness, and anxiety (32-37). The first aid treatment of hypoglycemia in conscious patients is the oral ingestion of 15-20 grams of glucose or carbohydrate-containing foods to raise blood glucose levels into the normal range. For the unconscious patients, glucose gel or jam spread inside a cheek’s bulge, or intravenous glucose should be given.

**2.1.4.2 Chronic complications**

The chronic complications of diabetes are divided into two groups as macroangiopathy and microangiopathy (38). The illustration of common chronic complications focusing on the hearing problems will also be discussed.

**2.1.4.2.1 Diabetic macroangiopathy**

The term of diabetic macroangiopathy is used for the lesion in large arterial wall associated with diabetes. The long term exposure with high blood glucose levels in diabetic patients can lead to the atherosclerosis and endothelial dysfunction of large vessel. The balance interaction between blood and vessel wall, which regulates the blood flow, hemeostasis, and vessel wall metabolism, is damaged in diabetes.

Generally, the atherosclerosis in diabetes is non-specific. It is observed to be more extensive throughout the circulation with more distal involvement of blood vessel. The process of atherosclerosis is probably similar to that observed in the non-diabetes, i.e smooth muscle cell proliferation, intimal thickening, excess collagen production, and medial calcification. The effects of diabetic macroangiopathy are predominant in three major sites of the cardiovascular system, consisting of coronary, cerebral, and peripheral arteries. The first clinical manifestation of this complication is often a specific event such as myocardial infarction and transient ischaemic episode (38-44).

**2.1.4.2.2 Diabetic microangiopathy**

Diabetic microangiopathy is the consequence of small vessel disease, contributing to the serious complications such as neuropathy, nephropathy, retinopathy, and hearing impairments.

**a. Diabetic neuropathy**

Diabetic neuropathy or nerve damage caused by diabetes is common and considered as a serious long-term complication of diabetes (45-48). This complication is classified into two broad types, consisting of diffuse and focal neuropathy. These two types have the different clinical characteristics.

The diffuse neuropathy is the most common type of diabetic neuropathy. It is sub-divided into distal symmetrical sensorimotor polyneuropathy (DSSP) and autonomic neuropathy. The symptoms of DSSP are typically mild to moderate neuropathic paresthesia and dysesthesia in the most distal extremities. In addition, the numbness in distal extremities can gradually develop. The autonomic neuropathy affects the autonomic nervous system of many organ systems such as cardiovascular system, gastrointestinal tract, genitourinary tract, sudomotor, adrenal gland, and iris.

The focal neuropathy is the result of a lesion in a single major nerve branch or root. The onset of this neuropathy type is sudden, and its symptoms normally abate in 1-2 months.

The pathogenesis of diabetic neuropathy can be directly related to many interrelated factors, including the long-term experiences with hyperglycemia, hypertension, hypercholesterolemia, and sometimes nutritional insufficiency (46-48). In short, the diabetic neuropathy can occur in the patients with type 1 and type 2 diabetes (48-50).

**b. Diabetic nephropathy**

Diabetic nephropathy causes a slow deterioration of kidney function, and it is the most common and serious complication of diabetes (51). The pathogenesis of this complication is not fully understood, but related to a combination of hyperglycemia, hypertension, and proteinuria. The persistent hyperglycemia can lead to a significant thickening of glomerular capillaries, which results in the alteration of intra glomerular hemodynamics.

The early stage of diabetic nephropathy is characterized by low levels of microalbuminuria. When the disease progresses to the next stage called “overt diabetic nephropathy”, the macroalbuminuria will develop. At the advance stage, the deterioration of kidney function occurs and contributes to the elevated serum creatinine levels, and renal failure, or end stage renal disease (ESRD). Commonly, the ESRD develops in 3-15 years after the overt diabetic nephropathy stage, and it is manifested by severe proteinuria and azotemia (51-54).

The diabetic nephropathy has no specific clinical signs. The poor glycemic control, hypertension, retinopathy, hypercholesterolemia, and diabetes duration more than 5 years, all are the predictors of diabetic nephropathy (55-57).

**c. Diabetic retinopathy**

Diabetic retinopathy is the most common and serious eye-related complication of diabetes. It is a progressive disease of retinal vasculature. The retina requires a continual blood supply, given through a network of capillaries for an effective function (58). The persistent high blood glucose levels and high blood pressure can lead to the thickening of capillaries basement membrane, blood vessels dysfunction, and retinal damage.

In the early stage of diabetic retinopathy, the patients may have only mild vision problems such as seeing spots or floaters in the vision, and night vision problem. In the advance stage, the patients may experience more symptoms of floaters, distortion, blurred vision, and/or blindness (59-61).

The diabetic retinopathy is related to the hyperglycemia, hypertension, smoking, and pregnancy. Moreover, the prevalence of diabetic retinopathy increases together with long-duration of uncontrolled diabetes. The primary prevention of this complication is the near-normal metabolic control, normal blood pressure, and abolish smoking (58-66).

**d. Hearing impairment**

Hearing loss is more common in diabetic patients. The relationship between diabetes and sensorineural hearing loss (SNHL) has been reported for more than a century. Many researchers agreed that the diabetes could induce the SNHL, but the reports of previous studies were debatable because the prevalence and degree of hearing loss were varied. Most of the hearing loss in diabetic patients, found in the audiometric studies, were bilateral, gradually progressive, and high frequency SNHL (67,68).

The pathogenesis of hearing impairments in diabetes results from the auditory alterations caused by the dysfunction of auditory system. However, the auditory alterations are not typical symptoms. These alterations are commonly related to the structures of inner ear, especially the cochlea, including Organ of Corti and structures of central auditory pathway from the auditory nerve to the auditory cortex (69). The Organ of Corti contains the outer and inner hair cells. The outer hair cells (OHCs) are responsible for amplification of sound, while the inner hair cells (IHCs) are responsible for mechanical electrical transduction of sound. OHCs amplify the mechanical signals delivered to IHCs, where it is switched into the electric potential to transfer the auditory information through the central nervous system into the auditory cortex. The auditory alterations in these inner ear structures is called sensorineural impairment (68,69).

The metabolic fluctuation caused by vascular complications in diabetic patients, who experienced high blood glucose levels, changed the micromechanics of inner ear (cochlea) and central nervous system, which then caused the hearing loss. The cochlear dysfunctions in diabetes could be attested by the histopathological studies of inner ear. Most of the studies showed the evidences as follows:

First, the vessels of basilar membrane (VBM) in individual with diabetes had a significant thickening of capillary endothelium walls in the basal, middle, and apical turns of cochlea. Second, there was a significant loss of OHCs in diabetic patients, especially in lower basal, upper basal, and lower middle turns of cochlea. The hair cells were recognized to be vulnerable by hypoxia. The loss of OHCs might be partially caused by microangiopathy, which was affected by oxidative stress that was a result of activation of polyol pathway in the hyperglycemia state. There was no relationship between the increase of thickening of VBM walls and loss of OHCs. There was also no significant decrease in the number of IHCs in any turns of cochlea. Third, there was a significant atrophy of stria vascularis, but no significant atrophy of spiral ganglion cells in most turns of cochlea (lower basal, lower middle, upper middle, and apical turn). Fourth, there was a significant thickening of capillary walls of stria vascularis, resulting in degenerative changes of Organ of Corti and reduction of cochlear function (70-72).

Furthermore, many histopathological studies of cochlea in diabetic animal models (such as Sabra line rats) reported a thickening of capillaries of basilar membrane (73), significant loss of OHCs (mainly in the basal and lower middle turns of cochlea) and certain parts of IHCs(74-76), atrophy of spiral ganglion cells (75-77), stria vascularis, and marginal cells in stria vascularis, and edematous changes of intermediate cells (76,78).

In conclusion, a thickening of vessels and capillaries of inner ear in diabetic animal models and in diabetic patients had been demonstrated (79), but there were still no report about significant differences in the cochlear vessel alterations between type 1 and type 2 diabetes. Nevertheless, other accelerating factors such as oxidative stress, apoptosis caused by hyperglycemia state, noise exposure, and hypertension could work synergistically to induce the pathological change in the OHCs (80-82).

Auditory neural dysfunctions (neuropathy) in diabetes could be demonstrated by the studies of central auditory pathway. Makishima and Tanaka (83) studied about the clinical pathology of diabetic neuropathy in humans by using optical microscopy and reported the atrophy of spiral ganglion neurons and demyelization of auditory nerve (8th cranial nerve) in four diabetic patients. Moreover, they described that the demyelination was also the primary lesion of peripheral nerves in most diabetic patients. Abnormalities in myelin metabolism might have an importance in pathogenesis of diabetic auditory neuropathy. Clicia and Carlos (84) studied the etiological factors of hearing loss in diabetes mellitus by using optical microscopy and observed the demyelination of auditory nerve via the changes of myelin sheath with small affection of axon, fibrosis of auditory nerve, and severe loss of cell in basal and middle turns of cochlea together with atrophy of spiral ganglion. In addition, they also found the decrease of number of auditory nerve fibers on the spiral lamina. Other findings were the reduction of total number of ganglion cells in ventral and dorsal cochlear nuclei, small loss of ganglion cells in inferior colliculus, superior olivary nucleus, and medial geniculate body. Nevertheless, the researchers did not investigate any specific affection in auditory cortex of both temporal lobes.

On the other hand, there were many studies, found neuropathy of cochlear nerve in diabetic patients by using the auditory brainstem response (ABR). The evoked potentials is the electrical signals from the central nervous system activated in response to the stimulation of a receptor. The ABR test has high sensitivity, but not specificity. This test is non-invasive test without any side-effects. If there is any damage in the nerve tract, it would result in the increase of latency, and decrease of amplitude of response. Most of these previous studies showed the abnormal results of ABR such as the prolonged absolute latencies and abnormalities of wave form morphology. These abnormalities in evoked potential studies indicated the abnormalities in central afferent and efferent pathways. The primary sensory neuron was more affected than the subsequent stages (85-88).

Luz et al. (89) studied the auditory impairment in patients with type 2 diabetes mellitus. They measured the auditory function of 94 patients by using ABR. The result showed an increase of wave V absolute latency and inter-wave I–V and III–V latencies. Moreover, the wave V absolute latency of right and left ears were asymmetry. The researchers described that the auditory brainstem response suggested the normal auditory nerve function, and the impaired neural conduction time within brainstem. Noorain (90) studied the patterns of auditory brainstem evoked response in 24 diabetic subjects with normal hearing. The result could be concluded that the diabetic patients had a significant delay in absolute latencies of wave I, III, and V, as well as inter-wave latencies III-V and I-V. The delay of neural conduction was caused by diabetes mellitus, and it could be evaluated by using ABR test before the symptoms of hearing loss actually appear. The prolongation of ABR latency in diabetic patients should be taken into consideration of auditory nerve damage.

At present, the prolongation of ABR latencies and inter-peak latencies (IPL) in diabetic patients has been observed in many studies. Many researchers agree that diabetic patients have a significant delay in the absolute latencies (especially wave III and V) and inter-wave I–V and III–V latencies, when comparing to the control group. The abnormality in neural conduction rapidity are more severe at the central auditory nerve, but less at the peripheral auditory nerve. The significant delay in absolute wave V latency and inter-peak latencies I-V and III-V demonstrate that diabetic neuropathy is diffuse and insidious particularly at the level of upper brainstem. The mechanisms contributed towards the delayed ABR latency are varied among the studies. At this point, the effects of ABR latencies might indicate the subclinical diabetic central neuropathy or subclinical auditory processing disorders in diabetic patients (91-93).

Moreover, the pathophysiology of central nervous system abnormalities was indistinct. Many causes were presumably, including the neural damage, hypoglycemic episodes, chronic hyperglycemia, angiopathy, and others unknown.

Since 1960, there were 3 theories about the pathogenesis of diabetic cochleopathy (a cause of hearing loss in diabetes) as follows: microangiopathy of inner ear, neuropathy of cochlear nerve, and combination of both. Presently, there are many significant reasons and evidences to accept that the microangiopathy detected in diabetic patients is the major root of hearing loss. In favor of this hypothesis, the histopathological findings of microvascular lesions of inner ear (cochlea) could be trusted, such as the thickness of vessels and capillaries of basal membrane and stria vascularis (91-98).

Generally, it can be clearly identified that the diabetes is a dangerous disease which burdens the people's life. Therefore, the patients have to change their habits in order to reduce these complications. Furthermore, the checked-up and followed-up with specialists are as important as taking care of oneself at home. It is better to search for more information and knowledge to have a deep comprehension in the disease and its treatment. These are the keys to perfectly prevent the diabetic complications.

## 2.2 Hearing loss in diabetes mellitus

### 2.2.1 Prevalence/ incidence of hearing loss in diabetes mellitus

The first consideration about a causal relationship between hearing impairment and diabetes was established in 1857 by Jordao et al (99-101). The first study showed effect of diabetes on hearing loss in an individual with incipient diabetic coma. Edgar et al. (102) discovered the first evidence of a recognizable pattern of hearing loss in diabetic patients, especially progressive bilateral high frequency SNHL. However, the first reported audiometric measurements in diabetes emerged in the 1950s (102).

Currently, many studies have reported the relationship between diabetes and SNHL, but the reports of prior studies are disputable. The fact of prevalence of hearing loss in diabetic patients still remains unclear and assorted (1,103-105).

Lerman et al. (103) conducted a cross-sectional study of adults under 50 years of age, compared the subject with type 2 diabetes to the control group without diabetes. They showed that the prevalence of mild to moderate hearing loss among those with diabetes was 21.7%, and significantly higher than the control group.

Rajendran et al. (1) found the increase of hearing loss in 60 individuals from 40 to 50 years of age with type 2 diabetes, compared with the control group of 60 non-diabetic healthy. The result showed the increase of highly significant bilateral mild to moderate sensorineural hearing loss and it was closer to higher frequencies, especially 4000, 8000 Hz. The incidence of SNHL amongst the diabetes was 73.3%, compared with 6.7% of the control at similar age. The duration of diabetes, either above or below 10 years, and the glycemic control were not found to have consequence in the incidence of hearing loss in the diabetic patients. However, Celik et al. (104) discovered that the incidence of sensorineural hearing loss significantly increased after 15 years of diabetes. Likewise, Lasisi et al. (105) reported the mean of hearing threshold levels in diabetic patients with diabetic duration less than 10 years was greatly better than those with more than 10 years duration. Moreover, other studies also supported that the hearing threshold levels became deteriorated as duration of diabetes increased (105-107).

Mozaffari et al. (108) evaluated the association of diabetes and sensorineural hearing loss in 80 non-elderly people with diabetes aged from 20 to 60, compared with the control group of 80 non-diabetic healthy with the same age and sex. The results showed that the incidence of SNHL amongst the diabetes is significantly higher than the control group (45% of diabetic subjects and 20% of control group).

Tay et al. (109) studied diabetes mellitus and hearing loss in 102 diabetic patients. The hearing thresholds data were compared with the control population groups who were non-diabetic healthy. The results showed a major difference in the average hearing thresholds between the diabetic subjects and the control groups. The diabetic subjects had higher prevalence of hearing loss and worse hearing threshold levels especially at low and mid frequencies.

Anil et al. (110) assessed the hearing acuity by audiometry in 39 type 2 diabetic patients 30 to 70 years of age and 25 subjects with non-diabetic controls at the same age and sex. The results showed significantly higher prevalence of SNHL among the diabetic patients at 73.7%, compared with 37.5% of the non-diabetic group

($p<0.005$). Most of diabetic subjects had bilateral SNHL (63.2%). High fasting blood glucose (FBG) and poor glycemic control but not the duration of diabetes had statistically significant effect toward the hearing loss.

Taziki et al. (111) studied the incidence of hearing loss among 50 diabetic and non-diabetic patients, aged from 15 to 75. The results showed the hearing loss was up to 16% in diabetic patients and 5% in non-diabetic group. Moreover, the results indicated direct relationship between the increasing age, duration of diabetes and hearing loss, while there was no significant difference with gender.

Mitchell et al. (112) studied the 5-year incidence and progression of hearing impairment in type 2 diabetes. There were 210 type 2 diabetic patients and 1648 non-diabetic participants, aged older than 49 years. The results showed that hearing loss was presented at 50.0% and 38.2% in type 2diabetic patients and non-diabetic control groups respectively. It demonstrated that incidence of hearing loss in type 2 diabetic patients was higher than non-diabetic group. Besides, the progression of hearing loss was significantly greater in subjects with newly diagnosed diabetes (69.6%) than in non-diabetic control groups (47.8%).

Abdulbari et al. (113) performed a cross-sectional study to find out the prevalence of hearing loss in 836 individuals with type 2 diabetes, aged 50 years or over (majority of the subjects were 50 – 59 years old). The hearing loss was diagnosed by using audiometer. The results showed that the prevalence of hearing loss in type 2 diabetic patients was higher in males (52.6%) than females (49.5%). The results confirmed the high prevalence of hearing loss in individuals with type 2 diabetes.

Bamanie and Al-Noury (114) performed an observational case-control study to investigate the prevalence of hearing loss among Saudi type 2 diabetic patients. The study was conducted in 109 individuals with type 2 diabetes, aged from 29 to 69, and 87 non-diabetes control with the same age and sex. The subjects with a history of conductive hearing loss (CHL), ototoxic medications, noise exposure, and positive family history of hearing loss were excluded. Hearing loss was assessed by using audiometer. The results indicated that the prevalence of hearing loss in Saudi type 2 diabetic patients were significantly higher than the observation in control groups especially at mid and high frequency. Besides, the results showed that the prevalence of hearing loss at low frequency in female with type 2 diabetes was higher when comparing to the female control groups. These evidences confirmed a strong correlation between type 2 diabetes and mid-high frequency hearing loss.

Diego et al. (115) studied the prevalence of hearing loss in type 1 diabetic patients to confirm the hearing threshold levels of individuals with type 1 diabetes. The study was conducted in 30 individuals with type 1 diabetes, aged from 18 to 55 (mean age at 25.9 years) and 30 non-diabetic participants (control groups), who had no family history of diabetes, aged from 18 to 55 (mean age at 26.56 years). The hearing assessment was done by conventional audiometry (250-8000 Hz.) and high-frequency audiometry (9000-16000 Hz.). The results showed statistically higher hearing threshold levels for both ears in the diabetic patients than the control groups at frequency 250, 500, 10,000, 11,200, 12,500, 14,000 and 16,000 Hz. The researchers concluded that there was definitely high incidence of hearing loss in type 1 diabetes.

Kathleen et al. (116) performed a cross sectional analysis study to verify the prevalence of hearing impairment among adults with diabetes in U.S. There were 399 adults with diabetes and 4,741 adults without diabetes (control groups), aged from 20 to 60, participating in this study. The hearing measurements were done by using audiometer. The researchers studied not only the frequency (low- mid and high) but also severity (mild to greater and moderate to greater) of hearing impairment. The low-mid frequency refers to 500, 1000, 2000 Hz., and the high frequency refers to 3000, 4000, 6000, 8000 Hz. The mild to greater hearing loss refers to the pure tone average greater than 25 dB HL, and the moderate to greater hearing loss refers to the pure tone average greater than 40 dB HL. The results showed that the low-mid frequency hearing loss of mild to greater severity was 21.3% and 9.4% in diabetic patients and non-diabetes respectively. Meanwhile, the high frequency hearing loss of mild to greater severity was 54.1% and 32.0% in diabetic patients and non-diabetes respectively. The researchers concluded that the adults with diabetes had higher prevalence of hearing loss than those without diabetes.

Mariusz et al. (117) evaluated the auditory function in relatively young type 1 diabetic patients, without evident hearing loss compared with the healthy participants. The study was conducted in 31 individuals with type 1 diabetes, aged below 45 years (mean age at 29.1 ± 7.1 years) with duration of diabetes less than 10 years (mean at 4.8 ± 2.7 years) and 26 non-diabetic participants at the same age. The pure tone audiometry was performed in all participants, and air-conduction was assessed for bone-conduction at the frequency of 125–12,000 Hz. and 250–6,000 Hz. The results demonstrated the mean hearing thresholds levels at frequencies 3,000–12,000 Hz. were significantly higher in diabetic patients than the control groups. The researchers concluded that the relatively young type 1 diabetic patients had higher incidence of hearing loss than non-diabetic.

Muhammad et al. (118) evaluated the frequency of SNHL in 17 type 1 diabetic and 93 type 2 diabetic patients, aged from 12 to 60 (mean age was 45.36 years). All diabetic patients underwent the audiometry to assess the hearing thresholds. The results showed that 79% of diabetic patients had SNHL. When considering each type of diabetes, 13 out of 17 type 1 diabetic patients (76%) had SNHL while 74 out of 93 type 2 diabetic patients (80%) had SNHL; thus, there was no significant difference in type 1 and type 2 diabetes in the severity of SNHL. Furthermore, the unilateral hearing loss was more common in type 1 while the bilateral was more common in type 2 diabetes.

Venkata et al. (119) performed the retrospective database review about the effect of diabetes on SNHL from 1989 to 2003 in order to identify the prevalence of SNHL in diabetic patients. The general history and audiometric data were collected. The electronic medical records of 12,575 diabetic patients and 53,461 non-diabetic control group, at the same age, were reviewed. The results showed that the prevalence of SNHL in diabetic patients was 13.1%, compared with 10.3% in non-diabetic control group.

In summary, the prevalence of hearing loss in diabetic patients are varied from 0 to 93% (84). The variation in prevalence or incidence of hearing loss may be caused by the different methods of evaluation, ages, nationality, characteristics, inclusion-exclusion criteria of participants, and study limitation. Nevertheless, most of researchers suggest the strong correlation and high incidence of hearing loss in the diabetic subjects.

### 2.2.2 Hearing loss characteristics in diabetes mellitus

Auditory neuropathy and microangiopathy in inner ear are ordinary affections in diabetes. The factors that may cause the neuropathy and microangiopathy are chronic metabolic disorders in diabetes, especially glucose, lipid and protein metabolism defects. Some previous studies showed that the microangiopathy, found in individual with diabetes, was associated to greater evidences with hearing loss. The microangiopathy may lead to hearing loss both directly and indirectly. In the direct way, it firstly interferes and/or obstructs the blood supply to the inner ear (cochlea), by decreasing the transportation and causing the walls of small arteries and capillaries thickened. For the indirect way, it is by the diminution of blood flow in vascular pathways of cochlea, resulting in the degeneration of auditory nerve because of deficient blood supply. The auditory alterations caused by diabetes damage the vasculature and neural system of the inner ear especially the cochlea, resulting in sensorineural hearing impairment.

Since 1980, Durmus et al. (120) demonstrated that the auditory neuropathy was the cause of hearing loss in diabetic patients and animal models. The type of hearing loss was SNHL and was significant in the mid and high frequencies. It could be described by the fact that diabetic microangiopathy affects the cochlea, mainly at the origin, basal turn of cochlea. The microangiopathy would be more progressive in patients with longer duration of diabetes and affected the apical turn as well. Consequently, it could induce the hearing loss at low frequency and/or across all ranges of frequencies.

At present the correlation between diabetes and hearing loss is widely interested by many researchers. Many studies demonstrate the strong relationship between diabetes and hearing loss. The most of previous studies have reported that the type of hearing loss, typically found in diabetes, is SNHL. However, the degrees of hearing loss in diabetic patients are varied from mild to severe, but deafness is rare. Nevertheless, it is widely believed that the bilateral gradually progresses from mild to moderate high frequency SNHL is typical characteristic of diabetes. Some studies have reported the low (121) and mid frequency hearing loss (109,122) and unilateral sudden hearing loss (123,124), while others have reported the across frequencies hearing loss (125).

Luz et al. (89) studied the auditory impairment in type 2 diabetic patients to evaluate the auditory function among 94 patients with type 2 diabetes (mean age at 50 years), and 94 participants with a good health at the same age and sex. The auditory function was assessed by using audiometer. The results showed the hearing threshold level at 8000 Hz. in patients with type 2 diabetes higher than the control groups. The researchers concluded that their findings were in the same direction as previous studies (1,102).

Veena et al. (126) performed a prospective study about the effect of type 2 diabetes on hearing. The main purpose was to find out the prevalence of SNHL in type 2 diabetes. The participants in this study were 75 individuals with type 2 diabetes (without hearing symptoms), aged from 30 to 50. The hearing thresholds were evaluated by using audiometry. The results revealed that the prevalence of SNHL among type 2 diabetes was 80%. Most of them had the gradual onset SNHL and a few cases had the sudden onset SNHL. From the diabetic patients with SNHL, 50% had slight (16-25 dB), 46% had mild, and 3.3% had moderate hearing loss. The hearing loss was more common in high frequency, but in few cases there were the mid frequency loss.

Pemmaiah and Srinivas (127) studied the hearing impairment in 110 individuals with type 2 diabetes (45 females and 65 males), aged from 20 to 75 with mean age of 46 years. The hearing evaluation was done by pure tone audiometry to ascertain the hearing function, degree, and type of hearing loss. The results showed that 43.6% of diabetic patients had bilateral SNHL especially at higher frequency (2000-4000 Hz.), 22.7% had moderate, 14.54% had moderately severe, and 6.36 % had severe hearing loss. It was also noticed that the hearing threshold levels increased for both air and bone conduction. It confirms that there is a high incidence of SNHL in individuals with type 2 diabetes.

Hidenari et al. (128) studied the correlation of impaired glucose tolerance and hearing loss in 699 middle-aged male (mean age at 52.9 years). The subjects were divided into 2 groups; 257 were classified as impaired glucose tolerance and 442 as the normal healthy groups. The hearing threshold levels were assessed by using audiometer. The results presented the hearing threshold levels at high frequency range (2–8 kHz.) in those with impaired glucose tolerance more than the normal healthy groups. However, there was a small difference of hearing threshold levels in impaired glucose tolerance and normal healthy groups at lower frequency range (0.25–1 kHz).

Susan et al. (125) investigated the characteristic natures of hearing impairment in aging with type 2 diabetes. There were 30 individuals with type 2 diabetes (15 females and 15males) and 30 individuals without diabetes (control groups), aged from 59 to 92 (mean age at 73 years). The hearing threshold levels were evaluated by using conventional audiometry (250-8000Hz.) and ultra-high-frequency audiometry (8000-14000 Hz.). The results showed that diabetic patients had the hearing threshold levels statistically and significantly higher than the control groups for all frequencies. The greatest hearing loss tended to be at the low frequencies and the elevation of hearing thresholds on the right ear was significantly higher than the left ear.

Suman et al. (129) studied the relationship between hearing loss and diabetes mellitus in 50 diabetic patients, aged below 50 years, and 25 non-diabetic healthy control at the same age and sex. The pure tone audiometry and tympanometry were done in all subjects to evaluate type and degree of hearing loss. The results showed 30% of diabetic patients had SNHL. Most of them (67%) had moderate, 27% had mild, and 6% had severe hearing loss, only 4% of control group had the hearing loss.

Nagaraj et al. (130) performed a prospective study of hearing loss in 102 type 2 diabetic patients, compared with 118 healthy controls at the same age and sex. The hearing loss was assessed by pure tone audiometry test. The results showed that 74% of diabetic patients had high frequency SNHL (at 2-8 kHz.). Most of them (55 %) had moderate, 26% had mild, and 19% had severe hearing loss. For the control groups, 36% had SNHL.

Karnire et al. (131) performed a prospective study to assess the type, degree, and audiometric pattern of hearing loss in diabetes. The study was conducted in 57 diabetic patients, aged older than 18 years, and 50 individuals without diabetes at the same age and sex. The pure tone audiometry was done in all subjects to evaluate the hearing threshold levels. The results revealed that the prevalence of SNHL in diabetic patients was 78.2%, compared to 38% in the non-diabetes control groups. Of diabetic patients with SNHL, 33.3% had moderate, 14% had severe, 14% had mild, 8.8% had slight (hearing threshold levels range 16- 25 dB HL), and 8.8% had profound hearing loss. The researchers concluded that the characteristics of hearing loss in diabetes were bilateral, symmetrical, gradually progressive, and mild to severe high frequency SNHL. The results were in accordance with many previous studies.

Pallavi (132) studied auditory acuity in type 2 diabetic patients to confirm the relationship between diabetes and hearing loss in 41 type 2 diabetic patients, aged from 35 to 55, compared with 41 normal and healthy control groups with the same age and sex. The pure tone audiometry was done in all participants to assess the hearing threshold levels. The results showed significant difference in hearing threshold levels at all frequencies from 250-8,000 Hz. between type 2 diabetic patients and control groups. This study confirmed the significant hearing loss in diabetic patients at all tested frequencies.

In conclusion, most audiometric findings of hearing test in diabetic patients show a mild to moderate high-frequency SNHL (133), while the patterns of the audiometric curves are varied in each study. It might be the effects of different variables such as characteristics, inclusion-exclusion criteria of participants, study limitation, duration of diabetes, blood glucose control, and location of hearing organ damaged in each diabetic patient. However, many researchers suggest that the sloping audiometric curves are most often seen in elderly diabetic patients, followed by flat audiogram, and then inverted scoop shape.

## 2.3 Risk factors for hearing loss in diabetes mellitus

The risk factors of hearing loss are everything that increases the likelihood of stimulating a symptom or condition. The hearing loss in diabetes is possible to develop together with or without the risk factors listed below. The risk factors of hearing loss in diabetes can be divided into two categories, including the external (environment) factors and internal factors.

### 2.3.1 External (environment) factors

Common factors that may damage or induce the loss of hair cells and nerve cells in the auditory system include:

**2.3.1.1 Occupational noises and noise exposure**

Noises are related to almost every work activity. Some work activities and/or environments are connected to particular high levels of noise. Either the excessive exposure to high levels of noise for a long time or the short-time and/or prolonged and repeated exposure to moderately loud noise all can lead to damage or change the physiology of inner ear, particularly the organ of cochlea, and especially the hair cells in the inner ear. Finally this will contribute to hearing loss. However, hearing loss onset can occur within the first 5 to 10 years of noise exposure (134). The occupational and noise exposure hearing loss can commence immediately or gradually, and may be temporary or permanent, depending on the intensity and frequency of the noise together with the duration of exposure. The hearing loss can be a small shift in the threshold, mild hearing loss, or total deafness. It usually starts to affect the pure-tone threshold at 3–6 kHz and can affect one or both ears. The occupations with the highest risk for hearing loss include those in mechanical engineering, construction, mining, manufacturing, transportation, agriculture, farming, and the military (134,135).

Abdulbari et al. (113) performed a cross-sectional study to find out the associated risk factors, contributing to hearing loss in 836 individuals with type 2 diabetes, aged 50 years or over. This study discovered that the excessive noise exposure for a long time was a major environmental factor, which was often related to SNHL in diabetic patients.

Nowadays, the correlation between noise and hearing loss has been demonstrated in many studies. Many researchers confirm that the occupational noise is a prevalent risk factor of hearing loss. There is a strong evidence, showing that it is meaningfully linked to health, especially hearing loss (135). This effect can occur in both diabetic patients and healthy people.

**2.3.1.2 Some medications**

Ototoxic drugs and chemotherapy may cause the damage in inner ear and can lead to hearing loss, balance problems, and tinnitus. Theoretically, the ototoxic drugs can harm the structures of the cochlea, especially hair cells, and/or the auditory nerve, which carries sound information to the auditory cortex. Hearing loss, caused by the damage of sensory cells and/or auditory nerve in the inner ear, is called the sensorineural hearing loss and it is usually permanent. Moreover, the ototoxic drugs can also harm the balance system, resulting in dizziness, unsteadiness, vertigo, sway and/or balance problems. Tinnitus is one of the effects of ototoxic drugs and it is frequently the first sign of hearing damage. Most of ototoxic drugs are in the group of antibiotics and aminoglycosides such as gentamycin, streptomycin, and neomycin. Moreover, high doses of aspirin and other pain relievers, antimalarial drugs, or loop diuretics can increase the risk of temporary hearing loss and tinnitus. The chemotherapy agents, such as cisplatin and carboplatin, can also damage the inner ear, and proceed the balance information by a toxin. In short, the ototoxicity commonly causes the permanent sensorineural hearing loss, especially at the ultra-high frequencies (136).

**2.3.1.3 Smoking and exposure to second hand smoke**

The scientists have accepted for almost 40 years that the hazard of smoking affects the hearing function. Many researches suggest that there may be three different pathophysiological mechanisms that can develop hearing loss in those with smoking habits and/or smoke exposure. The first mechanism may be associated with the hypoxia (deficiency of oxygen) because the nicotine and carbon monoxide may unfavorably consume the oxygen levels in the inner ear, especially cochlea, which is watery and where blood supplied. When the oxygen is drained, the damage of tissue in the inner ear will appear. The second mechanism is associated with the interplay between nicotine and neurotransmitters in the auditory nerve. It is described that nicotine impairs the neurotransmitters which serves as chemical messengers to correctly inform the brain what sound information is occurring inside the auditory nerve. The third suspected mechanism is associated with adolescent smoking. The researcher discovered that the mechanisms within the auditory nerve are not completely developed until late adolescents. Then it is believed that the auditory nerve pathways are particularly vulnerable to be damaged during adolescent period (137).

The smokers and exposure to second hand smoke increase the risk factors of serious health problems, associated with diabetes. Individuals with diabetes or pre-diabetes are already at high risk to develop the cardiovascular disease, a group of conditions affecting the heart, blood vessels, and blood circulatory system.

The pathogenesis of hearing loss in diabetes describes that the smoking affects the hearing of diabetic patients in many ways. It directly contributes to double the risk of developing the cardiovascular disease that can cause auditory nerve damaged, and narrow or damage the small blood vessels and capillaries (microangiopathy) in the inner ear, and also reduce the amount of oxygen (hypoxia) arrived the tissues of inner ear. Indirectly, smoking can induce high blood glucose levels to damage the small blood vessels in the inner ear, harm the blood flow to the cochlea, or change the blood consistency. All of these evidences are associated with the likelihood of hearing impairment, especially at the high frequency range (138).

### 2.3.2 Internal factors

Common factors that may contribute to hearing loss in diabetic patients include:

#### 2.3.2.1 Aging

Age-related hearing loss is also known as presbycusis. The damage of hearing structures and auditory nerves is caused by various origins over the years rather than biological degeneration (aging) alone. The age-related hearing loss is not recognized as a single cause. Mostly it is generally caused by the alteration in hearing structures of inner ear, especially the tiny organs, responsible for transmitting sound to the brain, called hair cells, the variation of blood flow to the inner ear, the impairment of auditory nerve which is responsible for hearing, and the alteration of auditory path way that delivers the speech and sound to the brain. All these alteration occurs as the age is increasing. Moreover, the family history of hearing loss, smoking, repeated exposure to loud sounds, diabetes, poor blood circulation, and even the exposure to sounds in daily life, all can contribute to the age-related hearing loss. The age-related hearing loss occurs slowly over time, and typically begins at high frequencies, and gradually progresses to the mid and then low frequencies.

Currently, there are some researches proving the relationship between diabetes (especially type 2) and age-related hearing loss such as a study of Mitchell et al (112). The participants in this study were 210 individuals with type 2 diabetes, aged 49 years or over and 1648 non-diabetic subjects at the same age. The results showed 50% of diabetic participants apparently had the age-related hearing loss, when comparing with 38.2% of non-diabetic participants.

The American Diabetes Association (139) suggested that there were more than 70% of high-frequency hearing loss and one third of low and/or mid frequency hearing loss among the individuals with diabetes, aged from 50 to 69. This evidence also suggested that individuals with diabetes might have the hearing loss when aged.

**2.3.2.2 Duration of diabetes**

Duration of diabetes is another factor related to the occurrence and severity of SNHL. Nevertheless, the role of diabetes progression and age-related hearing loss should be considered more carefully. Many studies prove that the duration of diabetes is significantly associated with SNHL. It means that the increase of hearing loss has a direct correlation with the duration of diabetes.

The study by Karnire et al. (131) in 2014 showed the high correlation between hearing loss and duration of diabetes. As the duration of diabetes increases, the occurrence of SNHL also increases. Mitchell et al. (112) studied the relationship between duration of diabetes in type 2 diabetic patients and SNHL. The results showed that the hearing sensitivity was statistically and significantly worse (higher hearing threshold levels) for all frequencies (maximum worse at 2 -6 kHz.) in diabetic participants. The relationship between duration of diabetes and severity of SNHL including higher hearing threshold levels at all frequencies was shown in the subjects with 10-year of diabetes or longer, compared to the subjects with less-than 10 years of diabetes. The researchers concluded that the duration of diabetes (more than 10 years) was related to the progression of SNHL.

Suman et al. (129) evaluated the possible contributing factors of SNHL in individuals with diabetes. The results proved that the diabetic patients with diabetes less than 9 years had mild SNHL, those with diabetes more than 9 years had moderate degree of SNHL, and those with diabetes more than 15 years were suffering with severe SNHL. The researcher concluded that the duration of diabetes was associated with degree of SNHL. In the same way, Pemmaiah and Srinivas (127) studied about the hearing loss in diabetes mellitus to evaluate the correlation between hearing impairment in type 2 diabetic patients and duration of diabetes. The results showed 42% of all diabetic patients had the duration of diabetes more than 10 years, and most of them (61.7%) at least showed mild SNHL. Moreover, 58% of all diabetic patients with duration of diabetes less than 10 years did not have SNHL. Moreover there was the significant correlation between duration of diabetes and SNHL at 2-4 kHz., but not at lower frequencies.

However, the reports of previous researches were debatable such as a study by Brown et al. (140) The results showed that the mean diabetes duration with occurrence of hearing loss was 7 years while Espana et al. (141) showed the mean diabetes duration to the hearing loss was 5 years.

In short, the mean diabetes duration to develop hearing loss in diabetic patients is still not in conclusion. The variation may be caused by the different methods, ages, characteristics, inclusion-exclusion criteria of participants, and study limitation. Nevertheless, most of researchers suggest that the duration of diabetes is significantly associated with increasing of SNHL.

**2.3.2.3 Complication of diabetes**

Diabetic complications, which include the retinopathy, nephropathy, coronary heart disease, and poor health, together with low level of high-density-lipoprotein (HDL) cholesterol, high cholesterol, hypertension (risk factor for atherosclerosis), are primarily related with vascular disease in diabetic patients. The vascular disease also comprises any aliments that affect the circulatory system in the body. The pathological changes in circulatory system caused by diabetic complications may lead to harm the vasculature and/or the neural system of inner ear, and then contribute to hearing loss.

Many investigations (142) of diabetes complications revealed that the hearing loss was related to nephropathy, but these evidences were indecisive in the aspect of pathophysiology. Recently, Kathleen et al. (143) studied the risk factors of hearing impairment in adults with diabetes. There were 536 diabetic patients, aged from 20 to 69 in the study. The results demonstrated that 67% of participants had high frequency SNHL, and 26% had the low and mid frequency hearing loss. Coronary heart disease doubled the prevalence of low and mid frequency hearing loss in diabetic patients. Moreover, 25% and 9% of diabetic patients with high frequency hearing loss were experienced by peripheral neuropathy and peripheral arterial disease respectively. The prevalence of low HDL was significantly higher in diabetic patients with SNHL at the low and mid frequency while the prevalence of high cholesterol was significantly greater in diabetic patients with hearing loss at the high frequency. This evidence supported the study of Gates et al. (146) who discovered the correlation between HDL and low-mid frequency hearing loss in women.

Moreover, blood glucose control (glycemic control) is associated with the occurrence and/or severity of SNHL. Long periods of experience with high blood glucose levels or hyperglycemia can induce atherosclerosis, a hardening of blood vessels throughout the body, especially the major organs such as the kidneys and heart. Then the small blood vessels and nerves in the inner ear, including the total hearing system, can be damaged, and lead to hearing loss. Many studies of diabetes complications suggested that the hearing loss was associated with glycemic control such as a study by Pemmaiah and Srinivas (127) who confirmed the significant relationship of high frequency hearing loss (2-4 kHz.) and HbA1c, and a study by Karnire et al. (131) who suggested the important correlation between HbA1c and hearing loss in diabetic patients. The similar results were found in the study done by Asma et a l(145). However Tay (109), Cullen et al. (121), and Kurien et al. (146) determined that the good glycemic control of diabetes could decrease the incidence of SNHL.

In short, any complications inducing the alteration of small blood vessels and auditory nerves in the hearing system can lead to SNHL. SNHL is the result of microangiopathic process, affecting the small blood vessels in the inner ear. Aging, duration, and severity of diabetes all are meaningfully related to the severity of SNHL and may be considered as the important defining factors of hearing loss in diabetic patients.

## 2.4 Audiological assessment in diabetes mellitus

Different audiological examinations help an audiologist to diagnose the natures of hearing impairment, and localize the site of lesion in the auditory system. Each of hearing test has different purpose. The most common investigations of hearing loss is clinical audiometry, while most common explorations of hair cell function is otoacoustic emissions (OAEs).

### 2.4.1 Clinical audiometry

Clinical audiometry is the gold standard measurement of hearing sensitivity to determine the lowest intensity of sound signal, which an individual can perceive the sound stimuli (the hearing threshold), and distinguish the different speeches of signal stimuli. The purpose of this test is to identify and diagnose the type and degree of hearing loss in all population (children, adults, and elderly). This hearing test is performed by electronic equipment, called an audiometer, and it is usually done in a soundproof-room by a trained clinician, known as an audiologist. The results of audiometry called an audiogram, a graphic representation of the intensity level, are plotted as the decibels hearing level (dB HL) in each frequency. The components of clinical audiometry include pure tone and speech audiometry.

Generally, the pure tone audiometry is executed in tandem with the speech audiometry. It refers to the previous segment about pure tone audiometry because the audiologist usually uses the pure tone audiogram as background information, which is helpful to examine the speech intensity in speech audiometry. However, the speech audiometry cannot be accurately predicted, based upon the pure tone thresholds.

The pure tone audiometry is the standard behavioral evaluation of hearing acuity, use of pure tones to assess the hearing threshold levels. The pure tones threshold levels indicate the lowest intensity of sound audible to an individual at 50% of the test in various sound frequencies. The frequencies of the tones are ranging from 250 to 8000 Hz. for air-conduction (AC) and from 500 to 4000 Hz. for bone-conduction (BC). The air-conduction signal is determined as a sound wave traveling through the air. The sound signals are presented via supra-aural, circum-aural, or inserted earphones. This manner of sound signal presentation evaluates the whole auditory system, starting from the outer ear, ear canal, tympanic membrane, middle ear system, cochlea, auditory nerve, auditory brainstem, and throughout auditory cortex. The impairment in one or more of these sections may cause a measurable hearing loss when testing pure tone air conduction audiometry. While the pure tone bone conduction audiometry stimulates the cochlea directly (by passing the outer and middle ear), the sound signals are presented via a bone vibrator, typically on the mastoid process. The pure tone bone conduction audiometry is used to ascertain the reflection of a cochlea and/or neural impairment. In other words, the bone-conduction is primarily used to distinguish between middle ear and inner ear which are associated with the hearing loss.

The speech audiometry is the measurement of capability to hear, understand, and discriminate the speeches. The speech stimulus is the monitored live voice (MLV). The tester's voice is picked up through an electronic microphone, managed by an audiometer and presented through a transducer such as the supra-aural earphones or inserted earphones. This speech audiometry test battery consists of two basic components; speech reception threshold and speech discrimination.

The speech reception threshold or speech recognition threshold (SRT) testing is the assessment of ability to recognize and repeat familiar words. The procedure is usually obtained by using spondee words, which are two syllabic words with equal emphasis on both syllables in standard pronunciation. The lowest intensity, at which a speech signal is intelligible enough to be recognized or identified and correctly repeated at 50% (usually two of four) of the words, is the SRT. The SRT has two basic roles. First, the SRT should concur with the pure tone average (PTA), which is the average of pure tone thresholds at 500, 1000, and 2000 Hz. Second, the SRT helps to define the intensity, used for speech discrimination testing.

The speech discrimination score (SDS) is also known as the speech recognition score (SRS), or word recognition score (WRS). The SDS testing is an important test in the audiometry test battery. It indicates the ability to hear, understand, discriminate, and correctly repeat at the typical conversational levels or most comfortable level (MCL). It is a standard method to use a presentation level at 30-40 dB above the SRT level or dB SL (sensation level). The SDS testing is usually obtained by using a standard list of mono syllabic words which are commonly comprised of 25 words, and it is indicated in percentage. The SD scores are used to distinguish the peripheral dysfunction (cochlear hearing loss) from central dysfunction (retrocochlear hearing loss). That is the SD scores of individual with cochlear hearing loss depending on the remainder of auditory nerve ability, while the individual with retro-cochlear hearing loss may still have a good or near normal pure tone thresholds, but encounter the difficulty in hearing and understanding speeches. This difficulty finally produces an effect of poor speech discrimination.

The hearing responses on the audiogram determine the degree of hearing for each ear. The classification of hearing loss is as follow; normal hearing is considered to be 0-25 dB HL, mild hearing loss from 26-40 dB HL, moderate hearing loss from 41-55 dB HL, moderately severe hearing loss from 56-70 dB HL, severe hearing loss from 71-90 dB HL, and profound hearing loss at above 90 dB HL.

In conclusion, the hearing loss is classified in three types as follows:

- If the AC and BC thresholds > 25 dB in any frequencies, AC thresholds concurs with BC thresholds (air-bone gap≤10 dB), and the SD scores depends on degree of hearing loss, defined to be associated with the lesions of cochlea and/or auditory nerve, it is known as the sensorineural hearing loss.
- If the AC thresholds > 25 dB, but < 60 dB, BC thresholds are normal (less than 25 dB HL) together with air-bone gap≥15 dB at least two frequencies, and a good SD score (good cochlear function). It defined to be associated with the lesions in the outer and/or middle ear that decreases the sound intensity, arriving the cochlea, it is known as the conductive hearing loss.
- If the AC thresholds > 25 dB, BC threshold is greater than 25 dB in only frequency and air-bone gap≥15 dB at least two frequencies, it is known as the mixed hearing loss. It means the combination of sensorineural and conductive impairment (147).

### 2.4.2 Otoacoustic emissions

Otoacoustic emissions (OAEs) are low intensity sounds measured in the external ear canal that reflects from inside the cochlea. It is originated along the basilar membrane by the electro motile (active) vibrations of OHCs in the organ of Corti, when the tympanic membrane receives energy of vibrations transmitted backwards through the middle ear from the cochlea. This energy is a product of unique and vulnerable cochlear mechanism, known as the cochlear amplifier, which helps induce the sensitivity and discrimination of hearing better. The OAEs work as an amplifier inside the cochlea to manage better hearing. Certainly, the normal OHCs function is necessary for the ideal normal auditory function. The OAEs have to use a probe with microphone to recording and measuring the results.

The OAEs are classified into two types; spontaneous and evoked OAEs. The spontaneous otoacoustic emissions are narrow band continuous emissions without any stimulus (spontaneously). These emissions are found in a majority of individuals with normal hearing. The clinical value of these emissions is limited because it is not presented in every individual with normal hearing and the absence of spontaneous otoacoustic emission does not suggest the OHCs dysfunction. Thus, they do not have any diagnostic and/or prognostic value as it is not a consistent feature in all normal hearing. The evoked OAEs have been recorded in emission response to various stimulus and can be divided into three types, including stimulus frequency OAEs (SFOAEs), transient evoked OAEs (TEOAEs), and distortion product OAEs (DPOAEs) (148).

The OAEs is an objective test. Its primary purpose is to investigate the cochlear status, specifically sensory hair cells (celled OHCs) function. Furthermore, OAEs test can be used as the hearing screening, monitoring for possible ototoxicity, differentiation of organic versus non-organic hearing loss (malingering hearing loss), and differentiation of cochlear versus retro-cochlear auditory dysfunction. The two types of evoked OAEs that are mostly used in clinical practice are TEOAEs and DPOAEs.

#### 2.4.2.1 Transient evoked otoacoustic emissions (TEOAEs)

TEOAEs response is evoked by a series of transient (very brief) stimulus such as a series of tone bursts or chirps or clicks (frequencies range between 2000 and 4000 Hz.), and presented at an intensity level of 80 dB SPL. A series of transient stimulus is sent into the ear through a probe that is inserted in the outer third of the ear canal. The probe includes the loudspeakers that originate the stimulus and a very sensitive microphone for measuring the OAEs result, reflecting from inside the cochlea during the stimulus presentations. An emission response is achieved within less than a minute. In the clinical evaluation, TEOAEs are usually used to screen the hearing in infants, and evaluate the cochlear function. The TEOAEs measurement is efficient to screen the hearing loss, because TEOAEs result is absent when the hearing thresholds levels are proximately 30-40 dB HL or higher.

**2.4.2.2 Distortion product otoacoustic emissions (DPOAEs)**

DPOAEs response is elicited by the simultaneous presentation of a pair of pure tones at frequencies F1 and F2. Those pure tones which stimulate the cochlea are labeled primaries. Lower tone is F1 and higher tone is F2. Another factor is the loudness level ratio of the primaries called L1 an L2. The studies investigate the loudness level ratio that yields the maximum DPOAE amplitude when L1 is higher than L2 and equal to 10 dB SPL (L1-L2=10 dB SPL). In the clinical practices, they are 55 and 65 dB SPL for L1 and L2 respectively. The DPOAEs can be measured across a frequency from 500 to 8,000 Hz., either higher or lower frequencies, depending on technique and parameter settings. The DPOAEs are the effects of intermodulation distortion products by non-linear aspect of the cochlear process in response to a pair of pure tones stimulus presented simultaneously at moderate intensity levels. Among the intermodulation processing, the cochlea generates a long series of components called the distortion products. The most prominent and clinical useful DPOAEs, of the primary intermodulation is 2f1- f2 and its ratio of a pair of pure tones frequencies is F2 / F1 = 1.2

DPOAEs are appropriated to advance the clinical investigation of adult patients. The DPOAEs measurements are more flexible and potentially more powerful than TEOAE. Therefore, it is usually used to evaluate the cochlear dysfunction, ototoxicity, and noise-induced damage. Even though, the DPOAEs measurement technique provides the opportunity to verify the early evidence of damage to OHCs either from noise or ototoxicity, the limitations of DPOAEs are known to be unable to detect the mild-moderate hearing loss of 26-50 dB HL. That is the DPOAEs will be absent for an individual with sensory hearing loss of 50 dBHL or more (149).

Currently, the advanced hearing technologies namely OAEs are extensively clinically applied in the pediatric and adult populations for many reasons. The clinical advantages of OAEs include the one-minute test time (usually less than a minute per ear), simple usage (can be applied by non-professional personnel), and non-invasive and objective test (unaffected by attention, cognition, and cooperation).

One of the most common clinical applications of OAEs is screening individuals who have the risk factor for hearing impairment. The indicators of OAEs screening results are ordinarily either “PASS” or “REFER”. The “PASS” result is displayed when the OAEs are present (> 6 dB above the noise floor) for the majority of test frequencies, while the “REFER” of OAEs screening result show as a risk factor for hearing impairment. Even though the “PASS” result of OAEs does not purely point to the normal hearing sensitivity, it helps a lot to sort out the individuals with serious degrees of hearing loss.

The OAEs are delicately sensitive to identify the OHCs dysfunction. Almost all attacks to the cochlea firstly damage the OHCs. The damage of small vessels or hypoxic cochlear deficiency can contribute to the reduction of OAEs’ amplitude. This can be assumed that the normal middle ear function with absence of OAEs indicates the evidence of cochlear (specific OHCs) dysfunction. In summary, the absence of OAEs reflects the cochlear dysfunction and damage of OHCs. The histopathological studies of inner ear confirm that the OHCs are significantly loss and the inner ear vascular damage is mostly found in diabetic patients. These evidences can be assumed that the OAEs are able to apply in the early detection of hearing impairment in diabetic patients.

# CHAPTER III
# MATERIALS AND METHODS

In this chapter, the study design, sample size, sample selection, inclusion and exclusion criteria of subjects were presented. All relevant general information and medical history of all subjects were reviewed. Instruments, methods, and procedure of data collection were discussed. Data analysis and statistic procedure were reviewed.

## 3.1 Study design

Prospective cross-sectional study was applied to compare the OAEs screening and clinical audiometry in diabetic patients without hearing symptom.

## 3.2 Sample size

PS Power and Sample Size Calculation Version 3.0 were used to perform power or sample size calculation in this study by using alpha error 0.05, beta error 0.2 (power of test 80%), and probability or efficiency of OAEs obtained from the studies of Francesco et al. The calculated sample size was equal to142 subjects for this study.

## 3.3 Sample selection

All subjects, known as diabetes mellitus patients, were diagnosed by the endocrinologist from OPD endocrine clinic at Ramathibodi hospital. They were enrolled in this study by their own permission.

## 3.4 Subjects

142 patients (71 were men and 71 were women) from out-patient endocrine clinic at Ramathibodi hospital, aged from 30 to 60 years old, did not have hearing symptom and were willing to join the study (signed in Informed Consent Form).

**Inclusion criteria**

- Diabetic patients were without hearing symptom.
- Answered "Often" less than 3 questions in the “Hearing Screening” questionnaire.
- Patients visited out-patient endocrine clinic at Ramathibodi hospital during official hours.
- Age from 30 to 60 years

**Exclusion criteria**

- Answered " Often " equal/more than 3 questions in the “Hearing Screening” questionnaire.
- Patients were suspected to have an outer and/or middle ear problem.

## 3.5 Instruments

Instruments used in this study included:

- “Hearing Screening” questionnaire applied by Rochester hearing and speech center.
- General information and medical history questionnaire of diabetic patients
- Portable otoscope
- OAEs screening : Accuscreen
- Audiometer : GSI 61
- Acoustic immittance measurement : GSI tymstar

## 3.6 Methods

All subjects underwent an interview for all general information, medical history and hearing examinations, including TEOAEs, DPOAEs, and clinical audiometry test. Biological calibration for AccuScreen PRO and GSI 61 Audiometer had been done weekly prior to data collection.

During the measurements of TEOAEs and DPOAEs, the subjects were instructed to rest in the supine position on a comfortable chair .This condition was to minimize postural muscle activities in neck and head. It reduced the internal noise. Criteria used to ensure a valid record during the test was the LED flashing green. If the LED was red, this indicated an error during testing, such as the probe was unstable, or artifacts were presented, which indicated the high environmental noise or a noisy subject.

The TEOAEs were tested by using AccuScreen PRO handheld Otoacoustic Emissions. The TEOAEs were elicited by brief stimulus such as clicks (the main frequency test was 2,000-4,000 Hz.). The stimulus level was 70-84 dB SPL (45-60 dB HL). AccuScreen was self-calibrating depending on ear canal volume. The probe was sealed into the ear with an ear-tip. In general, the recording of all OAEs required that a sensitive and low noise microphone would be sealed in the external ear canal. The microphone recorded the sound presented in the external ear canal in response to the acoustic stimulus. The strong result of TEOAEs indicated that the audiogram (either all or some parts) had the hearing threshold levels better than 25 dB HL, and correlated best with the good hearing in mid-frequency range. The result by the AccuScreen PRO was either given a “PASS” or a “REFER”. It was not possible to rely on the TEOAEs spectrum to predict the threshold levels by frequency. The TEOAEs were well suited and widely accepted for the hearing screening purpose.

The DPOAEs were tested by the same equipment as TEOAEs. The difference was the stimulus of the test with two simultaneous pure tones (f1,f2). The stimulus were known as primary tones. The stimulus level (L1/L2) pair was 59/50 dB SPL in f1,f2 respectively. DPOAEs were distorted in the sense that they were not presented in the eliciting pure tone stimuli. The most frequently measured distortion product was at the frequency 2f1-f2; although, the cochlea also produced the distortion product at other frequencies. The 2f1-f2 distortion product was the largest one, and it was the only one utilized for the clinical purposes now. The test frequencies were 2000, 2500, 3200, and 4000 Hz. The sequence of the test frequencies was as follow; 2500, 3200, 4000, and 2000 Hz. respectively. Accordingly, The DPOAEs could give better frequency with specific impression of cochlear integrity than TEOAEs, and were well suited to monitoring the cochlear function.

Clinical audiometry was tested by using a GSI 61 Audiometer. Pure tone thresholds were obtained from 250-8,000 Hz. for air-conduction and from 500 to 4000 Hz. for bone-conduction. The speech audiometry was performed, with the use of electronic microphone equipment, by both pure tone and speech audiometry in a sound-proof room.

All the tests were free of charges and caused no harm or any pain to subject.

## 3.7 Procedures

3.7.1 Patients would be informed about the research information and objectives, and signed the consent to participate in the study.

3.7.2 Subjects filled in the “Hearing Screening” questionnaire. If the answer showed " Often " less than 3, then continued to 3.7.3

3.7.3 Otoscopic examination. If outer and/or middle ear problem was suspected, they would be advised to see ear nose throat (ENT) doctors for appropriate treatment.

3.7.4 Filled in general information and medical history questionnaire**.**

3.7.5 Performed the TEOAEs and DPOAEs screening in sound proof room.

3.7.6 Performed the routine audiometry included pure tone air-conduction at frequency 250-8,000 Hz., pure tone bone-conduction threshold at frequency 500-4,000 Hz., speech reception threshold (SRT)., the speech discrimination (SD) in sound proof room.

3.7.7 If the audiogram showed air-bone gap (PTA at 500, 1,000, 2,000 Hz.) greater than or equal to 15 dB, the acoustic immittance measurement would be performed by using 226 Hz. probe tone and ipsilateral acoustic reflex at 500, 1,000, 2,000 Hz. to support a hearing test diagnosis.

3.7.8 The data would be collected and analyzed.

3.7.9 Diabetic patients with hearing loss would be advised to see ENT doctors for appropriate treatment.

## 3.8 Statistical analysis

The descriptive statistics, including mean, SD, and percentages, were analyzed to describe the subject's characteristics, duration of diabetes, and clinical data of diabetes (duration of treatment, FBS status, latest FBS levels, and etc.)

The main focus of this study was to examine the sensitivity and specificity of OAEs device measurement (both TEOAEs and DPOAEs), comparing to the outcome of clinical audiometry.

The diagnosis test, contingency table would be used to find out the efficiency of OAEs device, comparing to the clinical audiometry, in term of sensitivity, specificity, accuracy, positive and negative predictive values (PPV and NPV), and positive and negative likelihood ratios (LR+ and LR-).

The statistical analysis would be performed by using STATA 13.0 software (College Station, TX USA) with the statistical significance considered at $p<0.05$.

# CHAPTER IV
# RESULTS

The purpose of this study was to evaluate the efficiency of OAEs' screening, comparing with clinical audiometry in diabetic patients without hearing symptom. The measurable results were presented by mean, standard deviation (SD) and percentages. The screening of TEOAEs and DPOAEs results were considered as "PASS" and "REFER", while the clinical audiometry results in hearing responses was an audiogram to determine the type and degree of hearing for each ear. The statistical analysis of data included the general information and medical history in all subjects. It was performed by STATA 13.0 software and diagnosis test, using the contingency table to find out the efficiency of OAEs device, comparing to the clinical audiometry, in term of sensitivity, specificity, accuracy, positive and negative predictive values (PPV and NPV), and positive and negative likelihood ratios (LR+ and LR-).

The subjects in this study were 142 diabetic patients from the out-patient endocrine clinic at Ramathibodi hospital who did not have the hearing symptom (71 were men and 71 were women), aged from 30 to 60 years, and were willing to join the study (signed in Informed Consent Form). The data were collected in the Speech and Hearing Clinic at Ramathibodi hospital during May to August 2014. The results were reported, according to the research questions of this study.

## 4.1 Baseline characteristic of subjects

Table 4.1 showed the baseline characteristic of all subjects. The mean and SD of age were 51.94 years (SD=6.39). The percentages of past occupations were as follows: civil servant 34.50 %, entrepreneur 24.65%, laborer 14.08%, officer 10.56%, agriculturist 6.34%, policeman, soldier 4.23%, state enterprises 3.52%, unemployed and retirement 2.11%. The percentages of current occupations were as follows: civil servant 30.28%, entrepreneur 20.42%, unemployed, retirement 19.72%, laborer

11.97%, officer 8.45%, policeman, soldier 3.52%, agriculturist 3.52%, state enterprises 1.41%, and others 0.70%. The mean and SD of diabetes duration were 9.83 years (SD=7.50) and duration of diabetes medical treatment were 9.41 years (SD=7.4) respectively.

Most of the subjects (62.68%) were able to control the FBS status with mean duration at 5.45 years (SD=5.49) and 37.32% were out of control with mean duration at 4.57 years (SD=5.08). The mean and SD of latest FBS was 140.6 mg/dL (SD=48.99). In relation to the acute complications, 17.61% of subjects had hypoglycemia, 10.56% had hyperglycemia, 0.70% had DKA, more than one complication had 4.92%, and none had 66.20%. Most of the subjects (69.01%) had no chronic complications, 10.56% had ophthalmopathy, 9.13% had multiple of chronic complication, 4.23% had nephropathy, 2.82% had coronary heart disease, 2.82% had peripheral nervous system disease, 0.70% had cerebrovascular disease, and others 0.70%.

Most of the subjects in this study were treated with oral medication at 59.15%, insulin injection at 13.38%, exercise and diet control at 2.82%, and combined treatment at 24.65%. In all subjects, 59.86% had no underlying diseases, while 40.14% had underlying diseases. The underlying diseases included the circulatory system at 38.83%, endocrine system at 4.71%, respiratory system at 3.53%, reproductive system at 3.53%, infection at 3.53%, immune system at 2.35%, multiple of underlying diseases at 37.68%, and others 5.85%.

Most of the subjects (70.42%) had no history of smoking, and 19.01% were in the trial period to quit and some already quitted. There were only 10.56% of smokers. For 71.13% of subjects, they had no experience of loud noise exposure, 16.90% had some experiences, and only 11.97% were often exposed to noise. For 9.86% of subjects, they had history of ear diseases and 90.14% had none. There were 85.92% of subjects who never had the hearing test, while there were only 14.08% who ever had the history of hearing test. The hearing loss was reported by 40.00% of subjects.

**Table 4.1** Baseline characteristic of subjects

| Variables | Number (%) (Total = 142 cases) |
|---|---|
| **Age**, years, Mean ±SD | 51.94 ± 6.39 |
| **Past occupation** | |
| civil servant | 49 (34.50) |
| policeman, soldier | 6 (4.23) |
| state enterprises | 5 (3.52) |
| officer | 15 (10.56) |
| laborer | 20 (14.08) |
| entrepreneur | 35 (24.65) |
| agriculture | 9 (6.34) |
| unemployed, retirement | 3 (2.11) |
| **Current occupation** | |
| civil servant | 43 (30.28) |
| policeman, soldier | 5 (3.52) |
| state enterprises | 2 (1.41) |
| officer | 12 (8.45) |
| laborer | 17 (11.97) |
| entrepreneur | 29 (20.42) |
| agriculture | 5 (3.52) |
| other | 1 (0.70) |
| unemployed, retired government official | 28 (19.72) |
| **Diabetes duration**, years,Mean±SD | 9.83 ± 7.50 |
| **Duration of diabetes medical treatment**, years,Mean±SD | 9.41 ± 7.41 |
| **Status of control FBS** | |
| control | 89 (62.68) |
| control duration, years,Mean±SD | 5.45 ± 5.49 |
| outoff control | 53 (37.32) |
| outoff control duration, years,Mean±SD | 4.57 ± 5.08 |
| **Latest FBS**, mg/dL,Mean±SD | 140.6 ± 48.99 |
| **Acute complications** | |
| hypoglycemia | 25 (17.61) |
| hyperglycemia | 15 (10.56) |
| DKA | 1 (0.70) |
| multiple of acute complication | 7 (4.92) |
| none | 94 (66.20) |
| **Chronic complications** | |
| cerebrovascular disease | 1 (0.70) |
| coronary heart disease | 4 (2.82) |

**Table 4.1** Baseline characteristic of subjects (cont.)

| **Variables** | **Number (%) (Total = 142 cases)** |
|---|---|
| **Chronic complications**(cont.) | |
| peripheral nervous system disease | 4 (2.82) |
| nephropathy | 6 (4.23) |
| ophthalmopathy | 15 (10.56) |
| other | 1 (0.70) |
| multiple of chronic complication | 13 (9.13) |
| none | 98 (69.01) |
| **Modalities of treatment** | |
| oral medication | 84 (59.15) |
| insulin injection | 19 (13.38) |
| exercise and diet control | 4 (2.82) |
| combined treatment | 35 (24.65) |
| **Underlying diseases** | |
| yes | 57 (40.14) |
| no | 85 (59.86) |
| **Types of underlying diseases** | |
| respiratory system | 3 (3.53) |
| circulatory system | 33 (38.83) |
| endocrine system | 4 (4.71) |
| reproductive system | 3 (3.53) |
| immune system | 2 (2.35) |
| infection | 3 (3.53) |
| other | 5 (5.85) |
| multiple of underlying diseases | 32 (37.68) |
| **Smoking** | |
| never | 100 (70.42) |
| trial and already quitted | 27 (19.01) |
| smoking | 15 (10.56) |
| **Noise exposure** | |
| rarely | 101 (71.13) |
| sometimes | 24 (16.90) |
| often | 17 (11.97) |
| **History of ear diseases** | |
| yes | 14 (9.86) |
| no | 128 (90.14) |
| **History of hearing test** | |
| never | 122 (85.92) |
| once | 20 (14.08) |

**Table 4.1** Baseline characteristic of subjects (cont.)

| Variables | Number (%) (Total = 142 cases) |
|---|---|
| **Duration of hearing test** | |
| within 6 mo. | 1 (5.00) |
| within 1 year | 2 (10.00) |
| more than 1 year | 17 (85.00) |
| **Result of hearing test** | |
| normal | 12 (60.00) |
| abnormal | 8 (40.00) |

## 4.2 Prevalence of hearing loss from audiogram in diabetic patients without hearing symptom

The clinical audiometry, the gold standard of hearing test, was the test of sensitivity of hearing, and used to indicate the hearing loss in this study. The hearing loss was considered when pure tone air and/or bone conduction thresholds were greater than 25dB in each ear. Table 4.2 showed the prevalence of hearing loss in diabetic patients without hearing symptom; 105 subjects (73.94%) had hearing loss, of which 84 subjects (59.15%) had hearing loss in both ears, 11 subjects (7.75%) had hearing loss in right ear, and 10 subjects (7.04%) had hearing loss in left ear. There were only 37 subjects (26.06%) had normal hearing. In summary, the prevalence of hearing loss from audiogram of diabetic patients without hearing symptoms was 73.94% and most configuration of hearing impairment in diabetic patients was bilateral high frequency (above 2kHz.) hearing loss (43.81%).

**Table 4.2** Prevalence of hearing loss in diabetic patients without hearing symptoms

| Hearing diagnosis | Number (%) (Total = 142 cases) |
|---|---|
| Normal hearing | 37 (26.06) |
| Hearing loss of right ear | 11 (7.75) |
| Hearing loss of left ear | 10 (7.04) |
| Hearing loss of both ears | 84 (59.15) |

## 4.3 The correlation between TEOAEs screening results and clinical audiometry

The efficiency of TEOAEs screening was analyzed by using the contingency table to find out the TEOAEs screening results, when comparing to the clinical audiometry. Table 4.3 showed the TEOAEs screening results. The sensitivity of TEOAEs in detection of hearing loss was 27% and 29% in right and left ear respectively, while the specificity was 96% and 92% in right and left ear respectively. The accuracy of TEOAEs was 50% and 69% in right and left ear respectively. The positive predictive value (PPV) was 93% and 87% in right and left ear respectively, while the negative predictive value (NPV) was 40% in both ears. The positive likelihood ratio (LR+) was 6.85 and 3.63 in right and left ear respectively, while the negative likelihood ratio (LR-) was 0.75 and 0.77 in right and left ear respectively.

**Table 4.3** TEOAEs and DPOAEs screening results in correlation with clinical audiometry

| Types of OAEs screening | Right ear(%) | Left ear(%) |
|---|---|---|
| TEOAEs | | |
| Sensitivity | 27 | 29 |
| Specificity | 96 | 92 |
| Accuracy | 50 | 69 |
| PPV | 93 | 87 |
| NPV | 40 | 40 |
| LR+ | 6 .85 | 3.63 |
| LR- | 0.75 | 0.77 |
| DPOAEs | | |
| Sensitivity | 66 | 69 |
| Specificity | 89 | 83 |
| Accuracy | 74 | 74 |
| PPV | 93 | 89 |
| NPV | 57 | 58 |
| LR+ | 6.00 | 4.06 |
| LR- | 0.38 | 0.37 |

* Abbreviations: PPV = Positive predictive value, NPV = Negative predictive value,
LR+ = Positive likelihood ratio, LR- = Negative likelihood ratio

## 4.4 The correlation between DPOAEs screening results and clinical audiometry

The efficiency of DPOAEs screening was analyzed by using the contingency table to find out the DPOAEs screening results when comparing to the clinical audiometry. Table 4.3 showed the DPOAEs screening results. The sensitivity of DPOAEs in detection of hearing loss was 66% and 69% in right and left ear respectively, while specificity was 89% and 83% in right and left ear respectively. The accuracy of DPOAEs was 74% in both ears. The positive predictive value (PPV) was 93% and 89% in right and left ear respectively, while the negative predictive value (NPV) was 57% and 58% in right and left ear respectively. The positive likelihood ratio (LR+) was 6.00 and 4.06 in right and left ear respectively, while the negative likelihood ratio (LR-) was 0.38 and 0.37 in right and left ear respectively.

## 4.5 The comparison of TEOAEs and DPOAEs screening results

The table 4.3 showed TEOAEs and DPOAEs screening results when comparing to the clinical audiometry. In both ears, the DPOAEs had more sensitivity than TEOAEs, according to statistical analysis while their specificity were similar. The accuracy test of DPOAEs was greater than TEOAEs, especially in the right ear. In both ears, PPV of DPOAEs and TEOAEs were very similar, but the DPOAEs had NPV more than TEOAEs. In both ears, the test of LR+ for both DPOAEs and TEOAEs were similar, but LR- of DPOAEs was more than TEOAEs.

The tests of DPOAEs and TEOAEs had high specificity in both ears. Although, they were only the hearing screening tests, their results were specific enough to confidently sort out the abnormality. However, the DPOAEs were more powerful and sensitive in detection the hearing loss problems than TEOAEs, according to the statistical significant differences. Ideally, the hearing screening test should have the high sensitivity and specificity. It could be concluded that the DPOAEs were more efficient for hearing screening test in diabetic patients than TEOAEs.

# CHAPTER V
# DISCUSSION

The main objective of this study was to evaluate the efficiency of OAEs screening (both TEOAEs and DPOAEs) in order to define the hearing impairment when comparing with the clinical audiometry in 142 diabetic patients without hearing symptom. All diabetic patients were diagnosed by the endocrinologist from the out-patient endocrine clinic at the Ramathibodi hospital. They were enrolled in this study by their own permissions. The data were collected by the OAEs screening and clinical audiometry, and then analyzed by STATA 13.0 software and the contingency table.

## 5.1 Hearing impairment in diabetic patients

The results of this study showed that patients history taking, may not be an effective method to detect the diabetic patients' hearing status. The answers of interview showed that the patients did not recognize any hearing problems, while the results displayed that there were up to 73.94% of these patients having the hearing loss. Remarkably, there were bilateral and unilateral hearing loss up to 59.15% and 14.79% respectively in this group.

Even though the hearing loss in diabetic patients was quite a common problem, but both patients and their families are not aware of this problem at all. It is because the diabetes, related to the hearing loss, has a gradual onset with progressive hearing loss (2,121), which probably has less effect on their listening abilities and communications in daily life. This is the reason why patients report that they do not have the hearing symptom, which then resulting in late diagnosis of hearing loss.

Our study was similar to many researches that found the high prevalence or incidence of hearing loss in diabetic patients. The study by Rajendran et al. (1) in 2011 showed the prevalence of SNHL amongst diabetic patients was up to 73.3%, compared with 6.7% of control group at the same ages. Moreover the result showed that bilateral mild to moderate SNHL were more common on higher frequencies, especially 4000-8000 Hz. The study by Muhammad et al. (118) in 2013 reported that 79% of diabetic patients had SNHL. When investigating into each type of diabetes, 76% of type 1 and 80% of type 2 diabetic patients had SNHL. Study by Abdulbari et al. (113) in 2008 showed that the prevalence of hearing loss in type 2 diabetic patients was higher in males (52.6%) than females (49.5%). The results confirmed the high prevalence of hearing loss in individuals with type 2 diabetes, and these evidences indicated the high prevalence/ incidence of hearing loss in diabetic patients.

The mean age of subjects in this study was 52 years, and the mean duration of diabetes was 9.83 years. The mean of latest FBS was higher than normal range (normal range 70-100 mg/dL), and more than 60% had the diabetic complications, accompanied with the high prevalence of hearing loss (73.94%). This hearing loss was probably the result of many risk factors which stimulated a symptom or condition as follows: aging or age-related hearing loss, duration of diabetes, out of control of blood glucose levels, and complications of diabetes.

Concerning aging or age-related hearing loss, such as study by Mitchell et al. (112) in 2009 demonstrated the relationship between type 2 diabetes and age-related hearing loss. The results showed that 50% of diabetic participants apparently had the age-related hearing loss when comparing with 38.2% of non-diabetic participants. Moreover, the American Diabetes Association (139) suggested that there were more than 70% had high-frequency hearing loss and one third had low and/or mid frequency hearing loss among the individuals with diabetes, aged from 50-69 years old. This evidence also suggested that the individuals with diabetes were found to have the hearing loss in accordance with increasing age.

Concerning duration of diabetes, many studies (112,127,131) demonstrated that the duration of diabetes was significantly associated with SNHL. That was the increase of hearing loss had a direct correlation with the duration of diabetes. For example, the study by Karnire et al. (131) in 2014 showed the high correlation between hearing loss and duration of diabetes. As the duration of diabetes increased, the occurrence of SNHL affected also increased. Mitchell et al. (112) studied the relationship between duration of diabetes in type 2 diabetic patients and SNHL. The results showed worse hearing sensitivity (higher hearing threshold levels) for all frequencies (maximum worse at 2-6 kHz.) in the diabetic participants with statistical significance ($p<0.05$). The relationship between duration of diabetes and severity of SNHL was shown in the subjects with diabetes for 10 years or longer together with higher hearing threshold levels at all frequencies, compared with subjects with diabetes for less than 10 years. Researchers concluded that the duration of diabetes (greater than 10 years) was related to the progression of SNHL. In the same way, Pemmaiah and Srinivas (127) studied about the hearing loss in diabetes mellitus to evaluate the correlation between hearing impairment in type 2 diabetic patients and duration of diabetes. The results showed 42% of all diabetic patients had duration of diabetes more than 10 years. Most of them (61.7%) showed at least the mild SNHL, while the remainder about 58% of all, having the diabetes less than 10 years, did not have the SNHL. Moreover there was the significant statistical correlation between duration of diabetes and SNHL at 2-4 kHz., but there was no significant correlation at lower frequencies.

Concerning out of control of blood glucose (glycemic control) or long term experience with hyperglycemia (high blood glucose levels), such as the study by Karnire et al. (131) suggested the significant correlation between HbA1c and hearing loss in diabetic patients. The similar results were found in the study by Asma et al. (145) However Tay (109), Cullen et al. (121), and Kurien et al. (146) determined that the good glycemic control of diabetes decreased the incidence of SNHL.

Concerning complications of diabetes, many investigations of diabetes complications, demonstrated that the hearing loss was related to diabetes complications. For example, the study by Kathleen et al. (143) in 2011 showed that the coronary heart disease was twice in diabetic patients with the prevalence of low and mid frequency hearing loss. Moreover, 25% of diabetic patients with high frequency hearing loss experienced the peripheral neuropathy, and 9% of them had the peripheral arterial disease. Prevalence of low HDL was significantly higher in diabetic patients who had SNHL at low and mid frequency, while the prevalence of high cholesterol was significantly greater in diabetic patients who had SNHL at high frequency. This evidence agreed with the study by Gates et al. (146) who discovered the correlation between HDL and low-mid frequency hearing loss in women.

Furthermore, the severity of diabetes was correlated with the increase of treatments. That was the patients with severity of disease required more than one treatment. This study showed the result with statistical significance ($p<0.05$) that the subjects who needed many treatments had higher percentages of hearing loss than the subjects with less severity of diabetes, who needed only one treatment.

In our study, diabetic patients with hearing loss will get a proper management. They are suggested to meet ENT specialists for completely diagnose and treatment. When the treatment is complete, patients are considered to fit the hearing assistive devices which suited with their hearing severity and depend on their needs in daily life.

In summary, it did not always mean that diabetic patients without hearing symptom had normal hearing. Therefore all diabetic patients should be aware of their hearing status, especially the elderly patients who confronted with the long period of diabetes, many diabetic complications, and long term of high blood glucose level condition. Severity of diabetes was found to be correlated with many complications. Whatever complications that induced the alteration of small blood vessels and auditory nerves in the hearing system could lead to the hearing loss. The hearing loss was the result of microangiopathic process, affecting the small blood vessels in inner ear. The aging, duration, and severity of diabetes were well related to the severity of hearing loss, and might be considered as the important defining factors of hearing loss in diabetic patients (120).

## 5.2 Correlation between TEOAEs screening results and clinical audiometry

The results of this study showed the efficiency of TEOAEs screening when comparing with the clinical audiometry. In Table 4.3, the sensitivity of TEOAEs in detection of hearing impairment was 27% and 29%, while the specificity was 96% and 92% in right and left ears respectively. The accuracy of TEOAEs was 50% and 69% in right and left ears respectively. The positive predictive value (PPV) was 93% and 87% in right and left ears respectively, while the negative predictive value (NPV) was 40% in both ears. The positive likelihood ratio (LR+) was 6.85 and 3.63, while the negative likelihood ratio (LR-) was 0.75 and 0.77 in right and left ears respectively.

TEOAEs screening had shown the low sensitivity, but the high specificity in both ears. In fact, the sensitivity was also called the true positive rate. It was related to the ability of test to identify a condition correctly. Therefore the low sensitivity of TEOAEs screening meant that there were the low percentages of patients with hearing impairment, who got a positive test result. In contrast, the specificity was also called the true negative rate sometimes. It was related to the ability of test to exclude a condition correctly. Therefore, the high specificity of TEOAEs screening meant that there were the high percentages of patients without hearing impairment, who got a negative test result. In the clinical application, the sensitivity aimed to discriminate the abnormality cases from the normal ones. From the result, the sensitivity of TEOAEs was 27% and 29% in right and left ears respectively. The researcher could explain that TEOAEs might not be suitable for the screening test because the low sensitive test meant that there were many chances to have the false negative results, and then more cases of disease might be missed.

TEOAEs had the moderate accuracy of test in both ears. The accuracy was the ability of a measuring instrument to give a true value, so TEOAEs had the moderate ability to give a true result. TEOAEs screening had the high PPV, but low NPV in both ears. The higher value of PPV meant the more ability that the test could predict that the patients had the hearing impairment. On the contrary, the low NPV result meant the less ability that the test could predict that the patients did not have the hearing impairment. In this study, it showed the NPV was 40% in both ears. That meant the confidence of test to predict the negative result was around 40%. Consequently, it might be more suitable to use the gold standard test (clinical audiometry) to definitely confirm the diagnosis of hearing impairment in the patients with opportunity of hearing impairment such as the old people and patients with chronic complications.

This screening method had the high LR+ in right ear, but low in left ear, while it had the low LR- in both ears. When the test result was positive, TEOAEs would have more ability to separate the patients with hearing impairment from the patients with normal hearing in the right ear than the left ear. The low LR- meant when the test result was negative, TEOAEs would have more ability to separate the patients with hearing impairment from the patients with normal hearing.

The purpose of this study was to identify the correlation between TEOAEs and clinical audiometry. In this hypothesis, the result of TEOAEs showed the correlation with audiometric results. That was when the audiometric result of diabetic patients showed some degree of hearing loss, TEOAEs result should be abnormal. However, the result of this study was not conformed to the hypothesis because the most of diabetes patients had a high frequency sensorineural hearing loss which usually was beyond 3 kHz. It was due to the fact that TEOAEs was a sensitive tool to detect the hearing impairment at mid frequency region. That fact was disclosed in 1978. Kemp's initial report of TEOAEs described their several properties. According to the report, when the click stimulus was used to elicit the response, the emissions waveform would be idiosyncratic and likely to be dominated by the different frequency components at the different minutes in the test time. Moreover, the main issue reported that the energy of emissions in frequency region near 1500 Hz. dominated the response to the acoustic click stimulus. That was the click elicit broad spectrum response was much stronger in the mid frequency region (150).

TEOAEs results from the ears with normal hearing were characterized by their individualities across the ears. After grouping the results, it was found that the frequency components of responses were not distributed equally. That was the percentages of frequency components would decrease while the frequency increased as described in the study by Robinette (151). The study investigated TEOAEs testing in 265 ears with hearing threshold levels better than 25 dB HL across frequency. The results showed the percentages of responses' distribution by frequency as 96%, 94%, 89%, and 76% in 1 kHz., 2 kHz., 3 kHz., and 4 kHz. respectively. The study of Moulin et al. (152) also reported the similar decrease in 135 ears with normal hearing. They found that TEOAEs occurrence was up to100% at 4 kHz., while TEOAEs occurrence decreased to 50% at 5 kHz. region. These evidences confirmed the predominance of emission in the 1-2 kHz. range, and this dominance would occur even in the ears with hearing loss. Although, the click elicit broad spectrum response was much stronger in the mid frequency region, the diabetic patients with high frequency SNHL still had the normal TEOAEs screening result. This was why the diabetic patients had "PASS" of

TEOAEs. This meant that TEOAEs had low efficiency in detecting the hearing loss among the diabetic patients in this study.

TEOAEs were the complex acoustic consequences that could be recorded in almost every person who had the normal hearing. They were present only when the subjective threshold levels were better than 30 dB HL (150). Thoroughly, when all hearing threshold levels from 0.25-8 kHz. were better than 20 dB HL, TEOAEs would be present in 99% of ears. At the hearing threshold ranging from about 25 to 35 dB HL, TEOAEs results were not clear. At the hearing threshold levels poorer than 40 dB HL, TEOAEs were absent in 100% of ears with peripheral hearing loss. In consequence, when the patients had the mild hearing loss, the results of TEOAEs measurement could be presented as “PASS”. This evidence was possibly one of the factors that conduced to the low efficiency of TEOAEs among the diabetic patients.

Another factor that possibly contributed to the low efficiency of TEOAEs among the diabetic patients in this study was the total of residual cochlea conduced to TEOAEs. It was the important factor in the detection (153). The diabetic patients could have the residual cochlea region at the response to mid frequency where the click elicit broad spectrum response was much stronger; even though, they had either low or high frequency hearing loss. In short, the results of TEOAEs measurement still could be presented as “PASS” despite of the configuration of hearing loss. This evidence was confirmed by Mathis et al. (154), who assessed the groups of subjects with isolated hearing loss at either high or low-mid frequency range. The researchers determined that the rate of TEOAEs detection was depended upon the width of frequency range of preserved hearing. Moreover, they also found that it was highly depended upon the preservation of hearing in mid frequency.

Furthermore, the influence of the best threshold on the presence of TEOAEs was also the possibility to contribute the low efficiency of TEOAEs in this study. If the hearing threshold levels were better than 25-30 dB HL at mid frequency, but the hearing threshold levels were poorer than 30 dB HL at either high or low frequency, TEOAEs could still be detected (despite of this configuration of hearing loss). Collet et al. (155) reported the results from 931 ears with similar conclusion concerning this influence of the best threshold on the presence of TEOAEs. Whenever overall hearing loss was greater than 45dB HL, TEOAEs could still be detected in some ears but only if that hearing threshold at any frequency from 0.25-8 kHz. was better than 40dB HL. The influence of the best threshold was also confirmed by Lind and Randa (156), who studied 32 individuals with either high or low-mid frequency hearing loss. The results showed that TEOAEs response would be present despite of the configuration of hearing loss if the hearing threshold was better than 25-30 dB HL at 2 kHz.

Some researchers (157) might recommend to use TEOAEs in the identification of hearing loss in screening program because the test was relatively quick and the zone of uncertainty was smaller than DPOAEs. However, the results from this study showed the low efficiency of TEOAEs screening among the diabetic patients due to the main reasons as follows:

- TEOAEs were present when the subjective threshold levels were approximately better than 30 dB HL since the results of this study showed the air conduction pure tone average (PTA) at 23 and 22 dB in right and left ears respectively; thus, the results of TEOAEs measurement could be present when the patients had the mild hearing loss.
- Most of the subjects had the high frequency SNHL, but TEOAEs elicit broad spectrum response was much stronger in the mid frequency region, so the diabetic patients who had the high frequency SNHL could have the normal result of TEOAEs screening.

## 5.3 Correlation between DPOAEs screening results and clinical audiometry

The efficiency of DPOAEs screening was analyzed by using contingency table to find out DPOAEs screening results, compared with the clinical audiometry. Table 4.3 showed DPOAEs screening results. In all subjects, the sensitivity of DPOAEs was 66% and 69% in right and left ears respectively, while the specificity was 89% and 83% in right and left ears respectively. The accuracy of DPOAEs was 74% in both ears. The positive predictive value (PPV) was 93% and 89% in right and left ears respectively, while the negative predictive value (NPV) was 57% and 58% in right and left ears respectively. The likelihood ratio positive (LR+) was 6.00 and 4.06, while the likelihood ratio negative (LR-) was 0.38 and 0.37 in right and left ears respectively.

That was DPOAEs screening had the reasonably high sensitivity and specificity in both ears. DPOAEs had the high accuracy of test and high PPV in both ears, but had moderate NPV. This screening method had the high LR+ in right ear, but low in left ear, and had low LR- in both ears.

A common measurement of DPOAEs was done by typically recording a function of frequency of the primary tones (across a range of frequencies). Therefore DPOAEs were particularly regarded as attractive because of their inherent frequency specificity. DPOAEs results offered more scopes to provide the information of cochlear function at the specific frequency on each cochlea region. There was no doubt of the relation between DPOAEs and outer hair cell physiology. The dysfunction of outer hair cell temporarily produced an effect of transient changes to DPOAEs. Conversely, the permanent damage was translated into the irreversible frequency specific damage, such as the outer hair cell damage, by the alteration of cochlea in diabetic patients.

DPOAEs were absent when the subjective threshold levels were poorer than 40 dB HL. The low levels of stimulation were used in this study. This could explain higher cut-off point at 35-45 dB HL of DPOAEs. When the patients had mild hearing loss, the results of DPOAEs' measurement could be presented as "PASS" alike TEOAEs. This evidence possibly was a factor, conducing to the decrease of sensitivity of DPOAEs among the diabetic patients in this study.

There was a significant correlation of DPOAEs amplitude and hearing threshold levels ($p<0.001$) (158). The efficiency of DPOAEs was described by Gorga et al. (158), who applied the statistical decision theory to find out which DPOAEs could be best used to predict the hearing loss by frequency. In 180 subjects, the authors found that the hearing threshold levels above and below 20 dB HL could be differentiated on the basis of DPOAEs amplitude for specific stimulus frequency. The best performance was observed at 4 kHz., and the poorest was at 0.5 kHz. This evidence confirmed that DPOAEs were more reliable to predict the hearing loss at high frequency (above 3 kHz.). From the previous section, 73.94% of patients in this study had the hearing impairment, and most of them had high frequency SNHL.

Therefore, this was the main reason that DPOAEs screening had the reasonably high sensitivity, specificity, accuracy, PPV, and low LR- in both ears for detection of hearing loss in diabetic patients.

DPOAEs were also used as the sensitive measurement of hearing loss in the experiments of animals and humans. The ototoxic substance, high levels of noise, or long time experience with noise exposure also largely impacted the mechanisms of cochlea which was responsible for the generation of DPOAEs.

On the other hand, the individuals with noise-induced hearing loss were compatible with the diabetic patients who had the hearing impairment because the characteristics of both hearing loss were similar. That was most audiometric findings of hearing test showed the high-frequency SNHL. The study by Harris et al. (159) investigated the effect of hearing loss on DPOAEs' results in individuals with noise-induced hearing loss. The results showed that DPOAEs were affected adversely when the hearing loss was present, but only for the frequency range restricted to the loss. These results offered the promise that the monitoring of DPOAEs in individuals exposed to the noise in workplace could be beneficial. Therefore, it was reasonable to expect that DPOAEs' measurements could be used to monitor the changes in human cochlea with similar process. For example, it was used to investigate the cochlear dysfunction or hearing impairment in diabetic patients, who had experienced the high blood glucose levels for a long time. These high blood glucose levels could change the micromechanics of inner ear (cochlea), especially microangiopathy of inner ear and auditory nervous system, and finally caused the hearing loss.

In addition, the general attributes of distortions generated in the cochlea by two pure tones stimulation had been explored extensively in both experimental animals and human subjects. The increasing results from these studies provided the strong evidences, supporting that DPOAEs had the clinical relevance to identify the hearing loss by frequency, and monitor the changes in cochlear functions.

DPOAEs were the objective test, providing the rigorous estimation of cochlear status, because of the ability of tonal stimuli to intentionally deliver a moderate amount of sound energy to the specific frequency region in the cochlea. DPOAEs had the best promise to predict the cochlear function at high frequency. Additionally, the results from this study indicated that DPOAEs' screening had the reasonably high sensitivity, specificity, accuracy, PPV, and low LR- in both ears, compared with the clinical audiometry, which was the gold standard of hearing test. Thus, DPOAEs were very convenient for the hearing screening in diabetic patient.

## 5.4 Comparison of TEOAEs and DPOAEs screening results

Table 4.3 showed TEOAEs and DPOAEs screening results, compared with the clinical audiometry. The results showed the differences of TEOAEs and DPOAEs screening results as follows:

In both ears, DPOAEs had more sensitivity than TEOAEs with significant differences; although, their specificity were similar. As a result, both DPOAEs and TEOAEs had the high specificity of test in both ears. However, the accuracy of DPOAEs was greater than TEOAEs, especially in the right ear. In both ears, DPOAEs had NPV more than TEOAEs, while their PPV were very similar. In the same way, the LR- of DPOAEs was more than TEOAEs, but their LR+ were similar in both ears.

Both TEOAEs and DPOAEs had different advantages and disadvantages. The main differences between TEOAEs and DPOAEs were the stimulus, which TEOAEs were measured in the presence of stimulating click while DPOAEs were measured in the presence of stimulating two tones, what the cochlea was doing while either TEOAEs or DPOAEs were measuring, which parts of the whole OAEs response were captured, and which parts were rejected. DPOAEs method rejected all the stimulus frequency OAEs presented in the response. In the clinical practice, there was only the 2f1-f2 distortion component of OAEs accepted by DPOAEs; although, the other components, which were easily accessible, could be proved to have the supplementary value. On the other hand, TEOAEs method captured all components of stimulus frequency (click stimulus) and its response was broad spectrum across frequency range of click stimulus.

Both TEOAEs and DPOAEs observed the cochlea in different conditions. The cochlea was a complex organ that behaved differently to every stimulus. Generally, TEOAEs were the cochlear response, which was observed between the stimulation of relaxation phase and the response collected simultaneously across a wide frequency range. The disadvantage of TEOAEs screening was that it failed to extract the response at high frequencies

The tonal stimuli used in DPOAEs technique offered more scopes to provide the information of cochlear function. A major advantage of DPOAEs technique was its ability to investigate the OAEs response up to high frequencies, while its disadvantage was that it was easily influenced by the low frequency noise at low frequencies. However, the benefit of using long duration pure tone stimuli needed for DPOAEs recording was that the response obtained was highly specific to the particular pattern of vibration set up in the cochlea by that particular stimulus frequency.

There was evidence, showing that TEOAEs result derived from a relative dispersed large portion of basilar membrane in the cochlea, and that their detection and frequency content were influenced by the status of whole cochlea. On the contrary, DPOAEs appeared to arise from a localized portion of basilar membrane, and in a specific region that responded to a specific frequency. If the goal of measurement was to monitor the damage in a specific frequency region, then DPOAEs should be considered.

There were the differences in frequency range over which TEOAEs and DPOAEs could be measured effectively. The click evoked response or TEOAEs were dominated by the component in mid frequency range. However, DPOAEs could be measured over a broad range of frequencies. Besides, it could be measured in the high frequencies more than TEOAEs. Gorga et al. (157,158) decided that both TEOAEs and DPOAEs performed the identification of hearing loss well at 2 kHz. TEOAEs were better than DPOAEs at 1 kHz., but DPOAEs were preferable at 4 kHz. Neither performed the emission at 0.5 kHz. well because the measurement was severely compromised by noise. This evidence indicated that TEOAEs were the best to detect the threshold elevation below 3 kHz. On the other hand, DPOAEs were the best above 3 kHz. Therefore, DPOAEs provided the useful information more than TEOAEs at high frequencies.

In conclusion, DPOAEs are more sensitive to discover the hearing problems than TEOAEs. Ideally, the hearing screening test should have the high sensitivity and specificity. As a result, if one emission type has to be selected for the clinical testing to identify the hearing loss in diabetic patients, DPOAEs may be preferable. Their measurements are in more specific frequency, especially the high frequency where the hearing loss in diabetes is more likely to occur.

# CHAPTER VI
# CONCLUSION

The purposes of this study was to compare the relationship between the hearing screening test (both TEOAEs and DPOAEs) and the clinical audiometry test in order to evaluate the efficiency of OAEs screening and compare with the clinical audiometry in diabetic patients without hearing symptom. Then the sensitivity and specificity of OAEs measurement were examined and compared to the outcome of clinical audiometry. The results of this study were discussed according to the research questions and data reported in the literature review. The results from this study suggested the following conclusions:

1. Diabetic patients had higher prevalence of hearing loss (73.94%).

2. From the outcome of clinical audiometry, the results showed that most configuration of hearing impairment in diabetic patients was bilateral high frequency (above 2kHz.) hearing loss (43.81% of diabetic patients with hearing loss).

3. DPOAEs measurement was more sensitive and specific to detect the hearing problems in diabetes.

4. It did not always mean that the diabetic patients without hearing symptom had the normal hearing. Therefore all diabetic patients should be aware of their hearing status and have annual hearing check.

## Recommendation

From the results of this study, some recommendation and future research study have been proposed.

1. Early detection of hearing loss in diabetic patients can be convenient with simple technique and less time consumption by DPOAEs screening.

2. The results of this study can reasonably develop a guideline to detect the hearing loss in diabetic patients.

3. The audiological screening for diabetic patients should be DPOAEs. In case the abnormal results were found, the clinical audiometry and/or ABR measurement of hearing test battery should be done in order to specify the type, degree, configuration of hearing loss, and site of lesion.

4. Future research study should be focused on correlation between complication of diabetes and severity of hearing loss, or correlation between variable risk factors and hearing loss in diabetes.

5. Finally, the project of hearing conservation or prevention of hearing impairment in diabetes should be proposed and implemented.

# REFERENCES


1. Rajendran S, Anandhalakshmi M, Mythili B, Viswanatha R. Evaluation of the incidence of sensorineural hearing loss in patients with type 2 diabetes mellitus. Int J Biol Med Res 2011; 2(4): 982-987.
2. Hirose K. Hearing Loss and Diabetes: You might not know what you're missing. Ann Intern Med 2008; 149(1): 54-55.
3. สำนักนโยบายและยุทธศาสตร์สำนักงานปลัด กระทรวงสาธารณสุข. ข้อมูลสถิติ [ออนไลน์] 2550 [อ้างเมื่อ 15 ธันวาคม 2556]. จาก http://bps.ops.moph.go.th/index.php?mod=bps &doc=5.
4. Ruencharoen S. Audiological findings in diabetes mellitus patients with and those without hearing symptom [Master Thesis in Communication disorders]. Bangkok: Mahidol University; 1999. [in Thai].
5. Bainbridge K, Hoffman H, Cowie C. Diabetes and Hearing Impairment in The United States: Audiometric Evidence from the National Health and Nutrition Examination Survey, 1999 to 2004. Ann Intern Med 2008; 149(1): 1-10.
6. Cheng YJ, Gregg EW, Saaddine JB, Imperatore G, Zhang X, Albright AL. Three decade change in the prevalence of hearing impairment and its association with diabetes in the United States. Prev Med 2009; 49(5): 360–364.
7. Ciulla TA, Amador AG, Zinman B. Diabetic retinopathy and diabetic machular edema: pathophysiology, screening and novel therapies. Diabetes Care 2003; 26: 64-653.
8. Jorgensen MB. The inner ear in diabetes mellitus; Histological studies. Arch Otolaryngol Head Neck Surg 1961; l74: 81-373.
9. Fukushina H, Cureoglu S, Schachern PA, Kusunoki T, Oktay MF, Fukushina N. Cochlear changes in patients with type 1 diabetes mellitus. Arch Otolaryngol Head Neck Surg 2005; 133: 6-100.

10. Makishima K. Arteriolar clerosis as a cause of presbycusis. Arch Otolaryngol Head Neck Surg 1978; 86: 6-322.

11. Booya F. Potential risk factors for diabetic neuropathy: a case control study. BMC Neurology 2005; 5: 24-32.

12. Andersson G, Melin L, Lindberg P, Scott B. Development of a short scale for selt-assessment of experiences of hearing loss: The hearing coping assessment. Scand Audiol 1995; 24: 147-154.

13. Rowley WR, Bezold C. Creating public awareness: state 2025 diabetes forecasts. Popul Health Manag 2012; 15: 11-54 .

14. National Diabetes Data Group. Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. Diabetes Care 1979; 28: 57-103.

15. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2010; 33(1): S62-S69.

16. American Diabetes Association. Report of Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 1998; 21(1): s5-19.

17. Gavin JR, Alberti KG, Davidson MB. Report of Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 1997; 20: 1183-1197.

18. World Health Organization. Definition, diagnosis, classification of diabetes mellitus and its complications. Geneva: WHO; 1999.

19. American Diabetes Association. Diabetes 2001 Vital statistics. Alexandra,VA: ADA; 2001.

20. Blood A, Hayes TM, Gamble DR. Register of newly diagnosed diabetic children. BMJ 1975; 3: 580-583.

21. Guyton AC, Hall JE. Textbook of Medical physiology. 11th Edition. Elsevier Inc, New Delhi. 2006.

22. Kaku K. Pathophysiology of type 2 diabetes and its treatment policy. JMAJ 2010; 53(1): 41-46.

23. Gonzalez EL, Johansson S, Wallander MA, Rodriguez LA. Trends in the prevalence and incidence of diabetes in the UK:1996–2005. J Epidemiol Community Health 2009; 63: 332-336.

24. Neil HA, Gatling W, Mather HM, Thompson AV, Thorogood M, Fowler G., et al. The Oxford community Diabetes study; evidence for an increase in the prevalence of known diabetes in Great Britain. Diabetic Med 1987; 4: 539-543.
25. Raju SM, Raju B. Illustrated medical biochemistry. 2nd Edition. New Delhi, India: Jaypee Brothers Medical Publishers ltd; 2010.
26. American Diabetes Association. Diabetes. Diabetes Care 2006; 29: 51–580.
27. Defronzo RA, Ferrannini E. The Triumvirate: Beta Cell, Muscle, Liver. A Collusion Responsible for NIDDM. Diabetes Care 1988; 37: 667-687.
28. Holt GI. Diagnosis, epidemiology and pathogenesis of diabetes mellitus an update for Psychiatrists. Br J Psychiatry 2004; 184: 55-63.
29. Eledrisi MS, Alshanti MS, Shah MF, Brolosy B, Jaha N. Overview of the diagnosis and management of diabetic ketoacidosis. Am Journal Med Sci 2006; 331(5): 51-243.
30. Kitabchi AE, Umpierrez GE, Fisher JN, Murphy MB, Stentz FB. Thirty years of personal experience in hyperglycemic crises: diabetic ketoacidosis and hyperglycemic hyperosmolar state. J Clin Endocrinol and Metab 2008; 93 (5): 52-1541.
31. Umpierrez GE, Smiley D, Kitabchi AE. Narrative review: ketosis-prone type 2 diabetes mellitus. Ann Intern Med 2006; 144(5): 7-350.
32. Kitabchi AE, Umpierrez GE, Murphy MB, Barrett EJ, Kreisberg RA, Malone JI. Hyperglycemic crises in patients with diabetes mellitus. Diabetes Care 2003; 26: 109-117.
33. Cetin M, Yetgin S, Kara A. Hyperglycemia, ketoacidosis and other complications of L-asparaginase in children with acute lymphoblastic leukemia. J Med 1994; 3(4): 29-219.
34. Sommerfield AJ, Deary IJ, Frier BM . Acute hyperglycemia alters mood state and impairs cognitive performance in people with type 2 diabetes. Diabetes Care 2004; 10: 40-2335.
35. Centofani M. Diabetes Complications: More than Sugar?. Science News 1995; 149: 421.

36. Guettier JM, Gorden P. Hypoglycemia. Endocrinol Metab Clin North Am 2006; 35(4): 753-766.

37. Seaborg E. Balancing Glucose Levels: hypoglycemia guideline. Endocrine News 2009; 34(5): 12-15.

38. Cryer PE. Hypoglycemia risk reduction in type 1 diabetes. Exp Clin Endocrinol Diabetes 2001; 109: 412-423.

39. Hepburn DA, MacLeod KM, Pell AC, Scougal IJ, Frier BM. Frequency and symptoms of hypoglycaemia experienced by patients with type 2 diabetes treated with insulin. Diabetic Med 1993; 10: 231-237.

40. Boyle PJ, Schwartz NS, Shah SD, Clutter WE, Cryer PE. Plasma glucose concentrations at the onset of hypoglycemic symptoms in patients with poorly controlled diabetes and in nondiabetics. N Engl J Med 1988; 318: 1487-1492.

41. Cryer PE. Hypoglycemia-associated autonomic failure in diabetes. Am J Physiol Endocrinol Metab 2001; 281: 1115–1121.

42. Cryer PE, Davis SN, Shamoon H. Hypoglycemia in diabetes. Diabetes Care 2003; 26: 1902–1912.

43. Klein R. Hyperglycemia and macrovascular and microvascular disease in diabetes. Diabetes Care 1995; 18: 68-251.

44. Schwartz CJ, Valente AJ, Spraque EA, Kelley JL, Cayatte AJ, Kerbacher JJ, et al. Pathogenesis of the atherosclerosis lesion: implication for diabetes mellitus. Diabetes Care 1992; 15(9): 67-1156.

45. The American Diabetes Association. Neuropathy (nerve damage) [online] 2010 [cited 2014 Dec 1]. Available from: http://www.diabetes.org/living-withdiabetes/complications/neuropathy/.

46. Amato AA. Peripheral neuropathy [online] 2012 [cited 2014 Nov 21]. Available from: http://www.accessmedicine.com/content.aspx?aID=9148461.

47. The AGS Foundation for Health in Aging. Diabetic neuropathy [online] 2002 [cited 2014 Nov 21]. Available from: http://www. healthinaging.org/ public_education/diabetes/neuropathy.php.

48. Kanji JN, Anglin RE, Hunt DL, Panju A. Does this patient with diabetes have large-fiber peripheral neuropathy. JAMA 2010; 303(15): 32–1526.

49. Chen W, Zhang Y, Li X, Yang G, Liu JP. Chinese herbal medicine for diabetic peripheral neuropathy. Cochrane Database Syst Rev 2013; 10: 709-796.

50. National Institute of Diabetes and Digestive and Kidney Diseases. Diabetic neuropathies: The nerve damage of diabetes [online] 2002 [cited 2014 Nov 10]. Available from: http://diabetes.niddk.nih. gov/dm/pubs/ neuropathies/neuropathies.pdf.

51. Ekinci EI, Jerums G, Skene A, Crammer P, Power D, Cheong KY. Renal structure in normoalbuminuric and albuminuric patients with type 2 diabetes and impaired renal function. Diabetes Care 2013; 36(11): 6-3620.

52. Hall JE, Henegar JR, Dwyer TM, Liu J, Da Silva AA, Kuo JJ. Is obesity a major cause of chronic kidney disease?. Adv Ren Replace Ther 2004; 11(1): 41-54.

53. Yip JW, Jones SL, Wiseman MJ, Hill C, Viberti G. Glomerular hyperfiltration in the prediction of nephropathy in IDDM: a 10-year follow-up study. Diabetes Care 1996; 45(12): 33-1729.

54. Chiarelli F, Gaspari S, Marcovecchio ML. Role of growth factors in diabetic kidney disease. Horm Metab Res 2009; 41(8): 93-585.

55. Rask-Madsen C, King GL. Kidney complications: factors that protect the diabetic vasculature. J Nat Sci Biol Med 2010; 16(1): 1-40.

56. Agarwal R. Vitamin D, proteinuria, diabetic nephropathy, and progression of CKD. Clin J Am Soc Nephrol 2009; 4(9): 8-1523.

57. Fried LF, Emanuele N, Zhang JH, Brophy M, Conner TA, Duckworth W. Combined angiotensin inhibition for the treatment of diabetic nephropathy. N Engl J Med 2013; 369(20): 903-1892.

58. Frank RN. Etiologic mechanisms in diabetic retinopathy. Ryan SJ 1994: 76-1243.

59. Crawford TN, Alfaro DV, Kerrison JB, Jablon EP. Diabetic retinopathy and angiogenesis. Curr Diabetes Rev 2009; 5(1): 8-13.

60. Rodriguez-Fontal M, Kerrison JB, Alfaro DV, Jablon EP. Metabolic control and diabetic retinopathy. Curr Diabetes Rev 2009; 5(1): 3-7.

61. Liew G, Mitchell P, Wong TY. Systemic management of diabetic retinopathy. BMJ 2009; 338: 441.

62. Klein BE, Klein R, Moss SE. Incidence of cataract surgery in the Wisconsin Epidemiologic Study of Diabetic Retinopathy. Am J Ophthalmol 1995; 119: 295–300.

63. Klein R, Klein BE, Moss SE. The Wisconsin epidemiologic study of Diabetic Retinopathy. Am J Ophthalmol. 1995; 102: 7-16.

64. Klein R, Klein BE, Moss MS. Visual impairment in diabetics. Am J Ophthalmol. 1984; 91: 1–8.

65. Klein R, Klein BE, Moss SE. Davis MD, DeMets DL. The Wisconsin epidemiologic study of Diabetic Retinopathy II. Am J Ophthalmol. 1994; 102: 6-520.

66. Klein BE, Moss SE, Klein R. Effect of pregnancy on progression of diabetic retinopathy. Diabetes Care 1990; 13: 34-40.

67. Lisowska G, Namyslowski G, Morawski K, Strojek K. Early identification of hearing impairment in patients with type 1 diabetes mellitus. Otol Neurotol 2001; 22: 316-320.

68. Taylor IG, Irwin J. Some audiological aspects of diabetes mellitus. J Laryngol Otol 1978; 92(2): 99-113.

69. Brender E, Burke AE, Glass RM. Audiometry. JAMA 2006; 295- 460.

70. Kariya S, Cureoglua S, Fukushimad H, Moritad N, Baylanc MY, MaedabY, et al. Comparing the cochlear spiral modiolar artery in type-1 and type-2 diabetes mellitus: A human temporal bone study. Acta Med Okayama 2010; 64: 375-383.

71. Lisowska G, Namyslowski G, Morawski K, Strojek K. Cochlear dysfunction and diabetic microangiopathy. Scand Audiol 2001; 30: 199-203.

72. Fukushima H, Cureoglu S, Schachern PA, Kusunoki T, Oktay MF, Fukushima N, et al. Cochlear changes in patients with type 1 diabetes mellitus. J Otolaryngol Head Neck Surg 2005; 133: 100-106.

73. Smith TL, Raynor E, Prazma J, Buenting JE, Pillsbury HC. Insulin-dependent diabetic microangiopathy in the inner ear. Acta oto-largnologica 1995; 105: 236-240.

74. Rust KR, Prazma J, Triana RJ, Michaelis OE, Pillsbury HC. Inner ear damage secondary to diabetes mellitus, II: changes in aging SHR/N-cp rats. Arch Otolaryngol Head Neck Surg 1992; 118: 397-400.
75. Raynor E, Robison WG, Garrett CG, McGuirt WT, Pillsbury HC, Prazma J. Consumption of a high-galactose diet induces diabetic-like changes in the inner ear. Arch Otolaryngol Head Neck Surg 1995; 113: 748-754.
76. Nakae S, Tachibana M. The cochlea of the spontaneously diabetic mouse, II: electron microscopic observations of non-obese diabetic mice. Arch Otorhinolaryngol 1986; 243: 313-316.
77. Ishikawa T, Naito Y, Taniguchi K. Hearing impairment in WBN/Kob rats with spontaneous diabetes mellitus. Diabetologia 1995; 38: 649-655.
78. Tachibana M, Nakae S. The cochlea of the spontaneously diabetic mouse, I: electron microscopic observation of KK mice. Arch Otorhinolaryngol 1986; 243: 238-241.
79. Kakarlapudi V, Sawyer R, Staecker H. The effect of diabetes on sensorioneural hearing loss. Otol Neurotol 2003; 24: 382-386.
80. Mcquen CT, Baxter A, Smith TL, Raynor E, Yoon SM, Prazma J, et al. Non-insulin-dependent diabetic microangiopathy in the inner ear. J Laryngol Otol 1999; 113: 13-8.
81. Wackym PA, Linthicum FH. Diabetes mellitus and hearing loss: clinical and histopathological relationship. Am J Otol 1986; 7: 176-182.
82. Boden G. Role of fatty acids in the pathogenesis of insulin resistance and NIDDM. Diabetes Care 1997; 46: 3-10.
83. Tanaka AK, Makishima K. Pathological changes of the inner ear and central auditory pathway in diabetes. Ann Otol Rhinol Laryngol 1971; 80(2): 28-218.
84. Clicia S, Carlos H. Diabetes mellitus as etiological factor of hearing loss. Rev Bras Otorrinolaringol 2005; 71(2): 14-208.
85. Durmus C, Yetiser S, Durmus O. Audiotry brainstem evoked responses in insulin-dependent (ID) and non-insulin –dependent (NID) diabetic subjects with normal hearing. Int J Audiol 2004; 43: 29-33.

86. Kakarlapudi V, Sawyer DR, Staecker H. The Effect of Diabetes on Sensorioneural Hearing Loss. Otol Neurotol 2003; 24(3): 6-382.
87. Al-Azzawi LM, Mirza KB. The usefulness of the brainstem auditory evoked potential in the early diagnosis of cranial nerve neuropathy associated with diabetes mellitus. Electromyogr Clin Neurophysiol 2004; 44(7): 387-394.
88. Bayazit Y, Bekir N, Gungor K, Kepekci Y, Mumbuc S, Kanlikama M. The predictive value of auditory brainstem responses for diabetic retinopathy. Auris Nasus Larynx 2000; 27: 219-222.
89. Luz M, Kathrine S, Juan M. Auditory Impairment in Patients with Type 2 Diabetes Mellitus. Arch Med Res 2005; 36: 507-510.
90. Noorain A. An evaluative study of auditory brain-stem evoked response patterns in diabetic subjects with normal hearing. Int J Diabetes & Metab 2011; 19: 113-115.
91. Das T, Kundu S, Mazumdar AK, Mukhopadhyay SC. Studies on central nervous system function in diabetes mellitus. J Indian Med Assoc 2001; 99(2): 86-87.
92. Diaz de Leon-Morales LV, Jauregui-Renaud K, Garay-Sevilla ME, Hernandez-Prado J, Malacara-Hernandez JM. Auditory impairment in patients with type 2 diabetes mellitus. Arch Med Res 2005; 36: 507-510.
93. Alexander M. Thoms SV. Mohan PK. Prolonged brainstem auditory evoked potential latencies in tropical pancreatic diabetics with normal hearing. Electromyogr Clin Neurophysiol 1995; 35(2): 95-98.
94. Al-Azzawi LM, Mirza KB. The usefulness of the brainstem auditory evoked potential in the early diagnosis of cranial nerve neuropathy associated with diabetes mellitus. Electromyogr Clin Neurophysiol 2004; 44: 387-394.
95. Costa OA. Inner ear pathology in experimental diabetes. Laryngoscope 1967; 7: 68-75.
96. Bays H, Mandarino L, DeFronzo RA. Role of the adipocyte, free fatty acids, and ectopic fat in pathogenesis of type 2 diabetes mellitus: peroxisomal proliferator-activated receptor agonsits provide a rational therapeutic approach. J Clin Endocrinol Metab 2004; 89: 78-463.

97. Raynor EM, Carrasco VN, Prazma J, Pillsbury HC. An assessment of cochlear hair – cell loss in insulin – dependent diabetes mellitus diabetic and noise-exposed rats. Arch Otolaryngol Head and Neck Surg 1995; 121: 6-452.

98. Marulo T. Perceptive hypoacusias in diabetes mellitus. Rev Laryngol Otol Rhinol 1975; 95(5): 71-253.

99. Triana RJ, Suits GW, Garison S, Prazma J, Brechtelsbauer B, Michaelis OE, et al. Inner ear damage secondary to diabetes mellitus. Arch Otolaryngol Head Neck Surg 1991; 117: 40-635.

100. Rust KR, Prazma J, Michaelis OE, Pillsbury HC. Inner ear damage secondary to diabetes mellitus. Arch Otolaryngol Head Neck Surg 1992; 118: 394-400.

101. Smith TL, Raynor E, Prazma J, Buenting JE, Pillsbury HC. Insulin-dependent diabetic microangiopathy in the inner ear. Laryngoscope 1995; 105: 40-236.

102. Carmen RE, Svihovec D, Gocka EF, Ermshar CB, Gay GC, Vanore JF. Audiometric configuration as a reflection of diabetes. Am J Otol 1988; 9(4): 33-327.

103. Lerman-Garber I, Cuevas-Ramos D, Valdes S, et al. Sensorineural hearing loss-a common finding in early-onset type 2 diabes mellitus. Endocr Pract 2012; 18(4): 549-557.

104. Celik O, Yalçin S, Celebi H, Ozturk A. Hearing loss in insulin dependent diabetes mellitus. Auris Nasus Larynx 1996; 23: 32-127.

105. Lasisi OA, Nwaorgu OGB, Bella AF. Cochleovestibular complications of diabetes mellitus in Ibedan, Nigeria. Int J Otorhinolaryngol 2003; 1325-1328.

106. Fangcha MA. Diabetes and Hearing Impairment in Mexican American Adults: a population-based study. Am J Otolaryngol1998; 112: 835-839.

107. Virtaniemi J. Hearing thresholds in Insulin dependent diabetes mellitus. Am J Otolaryngol 1994; 108: 837-841.

108. Mozaffari M, Tajik A, Ariaei N, Ali-Ehyaii F, Behnam H. Diabetes mellitus and sensorineural hearing loss among non-elderly people. East Mediterr Health J 2010; 16(9): 952-947.

109. Tay HL, Ray N, Ohri R, Frootko NJ. Diabetes mellitus and hearing loss. Clin Otolaryngol Allied Sci 1995; 20(2): 4-130.

110.Anil HT, Anil Kumar AS, Lakshmi SR, Swathi RK. A Study on Sensori-Neural Hearing Loss in Patients of Type 2 Diabetes Mellitus. Int J Eng Sci Res 2014; 5(3): 2277-8179.

111.Taziki MH, Mansourian AR. The Comparison Of Hearing Loss Among Diabetic And Non-Diabetic Patients. J Clin Diagn Res 2011; 5(1): 88-90.

112.Mitchell P, Gopinath B, McMahon CM, Rochtchina E, Wang JJ, Boyages SC, Leeder SR. Complications Relationship of Type 2 diabetes to the prevalence, incidence and progression of age-related hearing loss. Diabetic Med 2009; 26: 483-488.

113.Abdulbari B, Ahmad HA, Sara MD, Abdulla A, Loida G. Association between hearing loss and Type 2 Diabetes Mellitus in elderly people in a newly developed society. Biomed Res 2008; 19 (3): 187-193.

114.Bamanie AH, Al-Noury HI. Prevalence of hearing loss among Saudi type 2 diabetic patients. Saudi Med J 2011; 32(2): 271-274.

115.Diego AM, Fernanda JM, Vinicius RF, Bianca Z, Angela R, Fabiano T, et al. Hearing loss prevalence in patients with diabetes mellitus type 1. Braz J Otorhinolaryngol 2012; 78(3): 15-105.

116.Kathleen EB, Howard JH, Catherine CC. Diabetes and Hearing Impairment in the United States:Audiometric Evidence from the National Health and Nutrition Examination Surveys, 1999–2004. Ann Intern Med 2008; 149(1): 1-10.

117.Mariusz D, Grażyna MN, Andrzej N. Involvement of the auditory organ in type 1 diabetes mellitus. Endokrynol Pol 2011; 62(2): 138-144.

118.Muhammad F, Ashfaque A, Zafar M, Abdul W. Frequency of Sensory Neural Hearing Loss (SNHL) in Type 1 and Type 2 Diabetic Patients. PJORL 2013; 29: 87-89.

119.Venkata K, Robert S, Hinrich S. The Effect of Diabetes on Sensorineural Hearing Loss. Am J Otolaryngol 2003; 24: 382-386.

120.Durmus C, Yetiser S, Durmus O. Auditory brainstem evoked responses in insulin-dependent (ID) and non-insulin-dependent (NID) diabetic subjects with normal hearing. Int J Audiol 2004; 43: 3-29.

121.Cullen JR, Cinnamond MJ. Hearing loss in diabetics. J Otolaryngol 1993; 107: 179-182.

122.Celik O, Yalcin S, Celebi H, Oztürk A. Hearing loss in insulin-dependent diabetes mellitus. Auris Nasus Larynx 1996; 23: 127-132.

123.Gawron W, Pospiech L, Noczynska A. Kozioro-wska E. Sudden hearing loss as a first complica- tion of long-standing Type 1 diabetes mellitus: A case re-port. Diabetic Med 2004; 21: 96-98.

124.Muhammad F, Ashfaque A, Zafar M, Abdul W. Frequency of Sensory Neural Hearing Loss (SNHL) in Type 1 and Type 2 Diabetic Patients. PJORL 2013; 29: 87-89.

125.Susan T, Frisina , Frances M, SungHee K, Robert F. Characterization of hearing loss in aged type II diabetics. Hear Res 2006; 211: 103-113.

126.Veena Pani MK, Swathi VM, Jasmine A. Effect of early onset type 2 diabetes mellitus on hearing. J Evol Med Dent Sci 2013; 46(2): 8880-8885.

127.Pemmaiah KD, Srinivas DR. Hearing loss in Diabetes Mellitus. Int J Collab Res Intern Med Public Health 2011; 3(10): 725-731.

128.Hidenari S, Takashi S, Hiroko Y, Teizo I. Type 2 diabetes and hearing loss in personnel of the Self-Defense Forces. Diabetes Res Clin Pract 2007; 75: 229-234.

129.Suman S, Rahul S, Yogesh A, Singh BK, Verma PC. Sensorineural hearing loss in diabetic patients. IJBAMR 2014; 3(3): 170-174.

130.Nagaraj BT, Ravi S, Ravi GC, Somasundar R. A one year prospective study of hearing loss in diabetes in general population. JAMA 2012; 3(2): 1-7.

131.Karnire NB, Sajid C, Ravi V, Abdul R. Clinical and Audiometric Assessment of Hearing Loss in Diabetes Mellitus. Int Union Sci Study 2014; 2(4): 1-16.

132.Pallavi P. Auditory acuity in type 2 diabetes mellitus. Indian J Physiol Pharmacol 2008; 28(4): 114-120.

133.Harner SG. Hearing in adult-onset diabetes mellitus. J Otolaryngol Head Neck Surg 198; 89: 7-322.

134.Albera R, Lacilla M, Piumetto E, Canale A. Noise-induced hearing loss evolution: influence of age and exposure to noise. Eur Arch Otorhinolaryngol 2010; 267: 71-665.

135.Lutman ME. What is the risk of noise-induced hearing loss at 80, 85, 90 dB (A) and above?. Occup Med 2000; 50(4): 274.

136.Skinner R, Pearson ADJ, Amineddine HA. Ototoxicity of cisplatinum in children and adolescent. Br J Cancer 1990; 61: 927-931.

137.Cruickshanks K, Klein R, Klein B, Wiley T, Nondah, D, Tweed T. Cigarette smoking and hearing loss: the epidemiology of hearing loss study. JAMA 1998; 279: 1715-1719.

138.Lustig LR. Nicotinic acetylcholine receptor structure and function in the efferent auditory system. The Anatomical Record. Part A. Discoveries in Molecular, Cellular, and Evolutionary Biology 2006; 288: 424-434.

139.American Diabetes Association. Standards of medical care in diabetes 2010. Diabetes Care 2010; 33(1): 11-61.

140.Sieger A, White NH, Skinner MW, Spector GJ. Auditory function in children with diabetes mellitus. Ann Otol Rhinol Laryngol 1983; 92: 24-237.

141.Espana R, Biurrun O, Lorente J, Traserra J. Hearing and diabetes. ORL J Otorhinolaryngol Relat Spec 1995; 57: 325-327.

142.Dalton DS, Cruickshanks KJ, Klein R, Klein BE, Wiley TL. Association of NIDDM and hearing loss. Diabetes Care 1998; 21: 1540-1544

143.Kathleen EB, Howard JH, Catherine CC. Risk Factors for Hearing Impairment Among U.S. Adults With Diabetes. Diabetes Care 2011; 34: 1540-1545.

144.Gates GA, Cobb JL, Agostino RB, Wolf PA. The relation of hearing in the elderly to the presence of cardiovascular disease and cardiovascular risk factors. Arch Otolaryngol Head Neck Surg 1993; 119: 156-161.

145.Asma M. Nor Azmi A. Mazita MB, Marina H, Salina M, Norlaila A. Single Blinded Randomized Controlled Study of the Effect of Conventional Oral Hypoglycemic Agents Versus Intensive Short-Term Insulin Therapy on Pure Tone Audiometry in Type II Diabetes Mellitus. Indian J Otolaryngol Head Neck Surg 2011; 63(2): 114-118.

146.Kurien M., Thomas K, Bhanu TS. Hearing threshold in patients with diabetes mellitus. Journal of Laryngology and Otology 1989; 103(2): 164-168.

147.Gelfand SA. Essentials of Audiology, 3rd ed. New York: Thieme Medical Publishers Inc; 2009.

148.Kemp DT. Stimulated acoustic emissions from within the human auditory system. J Acoust Soc Am 1978; 64: 91-1386.

149.Hall WH. Handbook of Otoacoustic Emissions. San Diego (CA): Singular; 2000.

150.Kemp DT. Stimulated acoustic emissions from within the human audiyory system. J Acoust Soc Am 1978; 64: 1386-1391.

151.Robinette MS. Clinical observations with transient evoked otoacoustic emissions with adults. Seminars in hearing 1992; 13: 23-36.

152.Moulin A, Collet L, Veuillet E, Morgon A. Interrelations between transiently evoked otoacoustic emissions, spontaneous otoacoustic emissions and acoustic distortion products in normally hearing subjects. Hear Res 1993; 65: 216-233.

153.Robinette MS. Frequency specificity of click evoked otoacoustic emissions for sensorineural hearing loss. Presentation to the American Speech-Language-Hearing Association; 1990 November.

154.Mathis A, De Min N, Arnold W. Transient evoked otoacoustic emissions in ears with preserved hearing in high, low or middle frequency ranges. HNO 1991; 39: 55-60.

155.Collet L, Levy V, Veuillet E, Truy E, Morgon A. Click evoked otoacoustic emissions and hearing threshold in sensorineural hearing loss. Ear Hear 1993; 14: 141-143.

156.Lind O, Randa J. Evoked otoacoustic emissions in high frequency vs. low/ medium frequency hearing loss. Int J Audiol 1989; 18: 115-123.

157.Gorga MP, Neely ST, Bergman BM, Beauchaine KL, Kaminski JR, Peters J, et al. A comparison of transient evoked and distortion products emissions in normal hearing and hearing impaired subjects. J Acoust Soc Am 1993; 94: 2639-2648.

158.Gorga MP, Neely ST, Bergman BM, Beauchaine KL, Kaminski JR, Peters J, et al. Otoacoustic emissions from normal hearing and hearing impaired subjects: Distortion product responses. J Acoust Soc Am 1993; 93: 2050-2060.

159.Harris FP, Probst R, Matefi L. Testing distortion products emissions in the Swiss hearing conservation program(SUVA). Presented at Effects of noise on hearing Vth international symposium, Gothenburg; 1994; Sweden.

# APPENDICES

# APPENDIX A

**แบบสอบถามเพื่อการวิจัย (1)**

**เรื่อง การศึกษาเปรียบเทียบผลตรวจคัดกรองการได้ยินและผลตรวจการได้ยิน**

**ในผู้ป่วยโรคเบาหวานที่ไม่แสดงอาการด้านการได้ยิน**

การใช้แบบสอบถามฉบับนี้ มีวัตถุประสงค์ที่จะประเมินและคัดกรองการได้ยินในผู้ป่วยโรคเบาหวานที่ประสงค์เข้าร่วมการศึกษาวิจัย คำตอบของท่านไม่มีผลกระทบต่อตัวท่านและ/หรือการรักษารวมทั้ง หน้าที่การงานของท่านแต่ประการใด แต่จะถูกใช้เพื่อเป็นประโยชน์ในการศึกษาวิจัยเท่านั้น

**วันที่.....................................................**

**ชื่อผู้ป่วย.................................................................... HN………….................**

❍ ผู้ป่วยตอบเอง ❍ ใช้วิธีการสัมภาษณ์

**คำชี้แจง** โปรดทำเครื่องหมาย ✓ ลงในช่องว่าง ที่เป็นจริงเกี่ยวกับสภาพการได้ยินของผู้ป่วยโรคเบาหวาน

| สภาพการได้ยิน | บ่อยครั้ง | บางครั้ง | ไม่เคย |
|---|---|---|---|
| 1. ได้ยินเสียงพูดแต่ไม่เข้าใจความหมาย | | | |
| 2. ต้องขอให้ผู้พูด พูดซ้ำ | | | |
| 3. มีเสียงดังในหู ปวดหู หรือเวียนศีรษะ | | | |
| 4. หากผู้พูดอยู่ข้างหลังหรือไม่เห็นหน้าผู้พูด จะฟังไม่เข้าใจ | | | |
| 5. บุคคลในครอบครัวแจ้งว่า คุณมักเปิดโทรทัศน์, วิทยุเสียงดังกว่าปกติ | | | |
| 6. เมื่อมีผู้พูดมากกว่า 1 คนในเวลาเดียวกันหรือในการสื่อสารเป็นกลุ่มย่อย จะฟังไม่เข้าใจ | | | |
| 7. มีความลำบากในการฟังเข้าใจเสียงพูดจากโทรทัศน์ หรือเสียงเพลง | | | |
| 8. ฟังไม่เข้าใจเมื่อสื่อสารทางโทรศัพท์ | | | |
| 9. ฟังไม่เข้าใจเมื่ออยู่ในสิ่งแวดล้อมที่มีเสียงรบกวน เช่น ในร้านอาหาร ในตลาด | | | |
| 10. บุคคลในครอบครัวหรือเพื่อนร่วมงานแจ้งว่า คุณพูดเสียงดังกว่าปกติ | | | |

หมายเหตุ : - หากตอบ “**บ่อยครั้ง**” ตั้งแต่ 3 ข้อขึ้นไป ควรเข้ารับการตรวจการได้ยิน พบแพทย์หรือนักแก้ไขการได้ยิน

- แบบสอบถามนี้ผ่านการตรวจสอบโดยอาจารย์และบุคลากรทั่วไป ช่วงอายุ 30-60 ปี

# APPENDIX B

**แบบสอบถามเพื่อการวิจัย (2)**

**เรื่อง การศึกษาเปรียบเทียบผลตรวจคัดกรองการได้ยินและผลตรวจการได้ยิน**

**ในผู้ป่วยโรคเบาหวานที่ไม่แสดงอาการด้านการได้ยิน**

แบบสอบถามฉบับนี้มุ่งที่จะสำรวจประเมินสถานสภาพและประวัติในผู้ป่วยโรคเบาหวานที่ไม่แสดงอาการด้านการได้ยินที่ประสงค์เข้าร่วมการศึกษาวิจัย คำตอบของท่านจะไม่มีผลกระทบต่อตัวท่านและ/หรือการรักษา รวมทั้งหน้าที่การงานของท่านแต่ประการใด แต่จะถูกใช้เพื่อประโยชน์ในการศึกษาวิจัยเท่านั้น

**วันที่……………………………………………**

**ชื่อผู้ป่วย…………………………………………………………..** **HN…………................**

❍ ผู้ป่วยตอบเอง

❍ ใช้วิธีการสัมภาษณ์

**คำชี้แจง** โปรดทำเครื่องหมาย ✓ ลงใน ( ) และกรอกข้อมูลที่เป็นจริงเกี่ยวกับตัวท่าน หน้าข้อความต่อไปนี้

1. เพศ : ( ) ชาย ( ) หญิง อายุ………..ปี
2. อาชีพ : อดีต…………………….................................ระยะเวลา……….…….. ปี

   ปัจจุบัน……………………........................... ระยะเวลา………….….. ปี
3. ระยะเวลาที่ได้รับการวินิจฉัยว่าเป็นโรคเบาหวาน………………….. ปี
4. ระยะเวลาที่ได้มารับการรักษาโรค ………………….. ปี
5. ปัจจุบันท่านควบคุมระดับน้ำตาลในเลือดได้หรือไม่ (มีค่า Fasting Plasma Glucose 70-130 mg/dL)

   ( ) ได้ เป็นระยะเวลา……………….. ปี

   ( ) ไม่ได้เป็นระยะเวลา……………….. ปี
6. ค่าของระดับน้ำตาลในเลือด (Fasting Plasma Glucose) ครั้งล่าสุด (ไม่เกิน 12 เดือนนับจากวันที่เข้ามาพบแพทย์ตามนัดครั้งสุดท้าย) ……………………………….........................................
7. ภาวะแทรกซ้อนเฉียบพลันของโรคเบาหวานในช่วง 12 เดือนที่ผ่านมา

   ( ) ภาวะน้ำตาลในเลือดต่ำ (Hypoglycemia)

   ( ) ภาวะน้ำตาลในเลือดสูง (Hyperglycemia)

   ( ) ภาวะเลือดเป็นกรดจากเบาหวาน (Diabetic ketoacidosis, DKA)

   ( ) อื่นๆ (ระบุ)…………………………………………………………………

8. ภาวะแทรกซ้อนเรื้อรังของโรคเบาหวาน

( ) ภาวะแทรกซ้อนของหลอดเลือดสมอง

( ) ภาวะแทรกซ้อนของหลอดเลือดหัวใจ

( ) ภาวะแทรกซ้อนของระบบประสาทส่วนปลาย

( ) โรคไตจากเบาหวาน

( ) โรคตาจากเบาหวาน

( ) อื่นๆ (ระบุ)…………………………………………………………………….

9. วิธีการรักษาในปัจจุบัน (ตอบได้มากกว่า 1 ข้อ)

( ) การใช้ยากินรักษาเบาหวาน

( ) ยาฉีด Insulin

( ) ไม่ใช้ยาเบาหวานใดๆ (ควบคุมอาหาร ลดน้ำหนัก ออกกายลังกาย)

10. ท่านมีโรคประจำตัวอื่นหรือไม่ (ระยะเวลาการเป็นโรคต้องมากกว่าหรือเท่ากับ 12 เดือน)

( ) มี (ระบุ)………………………………………………………………………

( ) ไม่มี

11. ประวัติการสูบบุหรี่

( ) ยังคงสูบอยู่ในช่วง 12 เดือนที่ผ่านมา นับจากวันที่มาตามนัดครั้งสุดท้าย

( ) เคยสูบ แต่เลิกสูบแล้ว

( ) ไม่เคยสูบ

12. ประวัติการสัมผัสเสียงดัง

( ) เป็นประจำ………………………………………………………………………..….

( ) บางครั้ง……………………………………………………………………………..

( ) นานๆครั้ง…………………………………………………………………………..

13. ประวัติโรคหูในอดีต

( ) มี (ระบุ)………………………………………………………………………………...

( ) ไม่มี

14. ท่านเคยได้รับการตรวจการได้ยินมาก่อนหรือไม่

( ) ไม่เคย

( ) เคย : ระยะเวลาที่ท่านเคยได้รับการตรวจการได้ยิน

( ) ภายใน 6 เดือนที่แล้ว ( ) ภายในปีที่แล้ว ( ) นานกว่า 1ปีที่ผ่านมา

15. ผลตรวจการได้ยินของท่านเป็นอย่างไร

( ) ปกติ ( ) ผิดปกติ

# APPENDIX C

**คณะแพทยศาสตร์โรงพยาบาลรามาธิบดี มหาวิทยาลัยมหิดล**
๒๗๐ ถนนพระราม ๖ แขวงทุ่งพญาไท เขตราชเทวี กทม. ๑๐๔๐๐
โทร. (๐๒) ๒๐๑-๑๐๐๐

**Faculty of Medicine Ramathibodi Hospital, Mahidol University.**
270 Rama VI Road, Ratchathewi, Bangkok 10400, Thailand
Tel. (662) 201-1000

**Documentary Proof of Ethical Clearance**
**Committee on Human Rights Related to Research Involving Human Subjects**
**Faculty of Medicine Ramathibodi Hospital, Mahidol University**

---

**No MURA2014/94 $N_1$ - May $_{15}$**

| | |
|---|---|
| **Title of Project** | Comparison of OAEs Screening and Clinical Audiometry in Diabetic Patients without Hearing Symptom |
| **Protocol Number** | ID 02 – 57 – 28 |
| **Principal Investigator** | Miss Veeraya Charlee |
| **New Title 1:** Approval : 11/05/2015 | Comparison of OAEs Screening and Clinical Audiometry in Diabetic Patients Without Hearing Symptom |
| **Official Address** | Communication Sciences and Disorders Faculty of Medicine Ramathibodi Hospital Mahidol University |

***The aforementioned project has been reviewed and approved by the Committee on Human Rights Related to Research Involving Human Subjects, based on the Declaration of Helsinki.***

| | |
|---|---|
| **Signature of Chairman Committee on Human Rights Related to Research Involving Human Subjects** | Pratak Oprasertsawat ……………… Prof. Pratak O-Prasertsawat, M.D. |
| **Date of Approval** | March 4, 2014 |
| **Duration of Study** | 9 Months |

# BIOGRAPHY

| | |
|---|---|
| **NAME** | Weeraya Charlee |
| **DATE OF BIRTH** | 1 February 1989 |
| **PLACE OF BIRTH** | Nakhon Ratchasima, Thailand |
| **INSTITUTIONS ATTENDED** | Mahidol University, 2007-2010<br>Bachelor of Science<br>(Communication Disorders)<br>Mahidol University, 2012-2015<br>Master of Science<br>(Communication Disorders) |
| **RESEARCH GRANTS** | The thesis partially support scholarship for academic year 2014 by Mahidol University Graduate Alumni Association<br>Grant to support graduate students in academic presentations in Thailand academic year 2015 by Mahidol University Student Services Section |
| **HOME ADDRESS** | Nakhon Ratchasima, Thailand<br>Tel. 087-3318153<br>E-mail : Berry_boo-@hotmail.com |
| **PUBLICATION / PRESENTATION** | The 34 th National Graduate Research Conference, Khon Kaen University, Thailand. |