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EVALUATION OF HEARING LOSS IN TYPE-2 DIABETES MELLITUS CORRELATING WITH HBA1C – A REVIEW

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ABSTRACT

Diabetes mellitus is an endocrinological metabolic disorder affecting insulin secretion or its action leading to insulin resistance. Disturbances in protein, carbohydrate and fat metabolism will occur due to hyperglycemia caused by insulin deficiency. The incidence of diabetes mellitus will increase from 200 milion worldwide in 2010 to 300 million by the year due to decreased awareness among the population. Moreover those diabetic patients who are not under control will have the morbid complications like cochleopathy, retinopathy, nephropathy, cardiovascular complications etc. The aim of this review article is to create awareness among the diabetic patients about the morbid diabetic cochleopathy which leads to irreversible bilateral sudden hearing loss. Henceforth it is advisable for the diabetic people to have their glycemic control in good condition so that they can be prevented from cochleopathy leading to hearing loss.

KEYWORDS: **Diabetes mellitus, Cochleopathy, Insulin.**

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INTRODUCTION

Diabetes mellitus is a disease which affects the insulin secretion or its action increases the blood glucose level with disturbances in the metabolism of fat, protein, and carbohydrate & therefore it is considered as endocrinological & metabolic disorder. About 10% of the total population, and about 1/5th of persons above the age of 50, suffer from this disease. It is a major cause for morbidity and mortality. Insulin deficiency leads to increased blood sugar level. In spite of this high blood glucose, the entry of glucose into the cell is inefficient. Hence, cells are dependant on insulin for entry of glucose. Insulin is a hypoglycemic hormone secreted by the beta cell of pancreas which decrease the blood glucose level by promoting glycogenesis, glycolysis, lipogenesis etc. thereby maintaining the normal blood glucose level.

Diabetes mellitus

The term is derived from the Greek words dia (=through), bainein (=to go) and diabetes literally means pass through. The disease causes loss of weight as if the body mass is passed through the urine. The Greek word, mellitus, means sweet, as it is known to workers, that the urine of the patients contain sugar. Diabetes mellitus is a disease known from very ancient times. Charaka in his treatise (circa in 400BC) gives a very elaborate clinical description of madhumeha (=sweet urine). Upon 11th century diabetes commonly diagnosed by Water tasters who drank the urine of those suspected of having diabetes; the urine of people with diabetes was thought to be sweet tasting. The Latin word for honey 'mellitus' is added to the term diabetes as a result. He had the vision that carbohydrate and fat metabolisms are altered in the disease. Early 19th century first chemical test developed to indicate and measure the presence of sugar in the urine.Qualitative test for urine sugar was perfected by Hermann Fehling (1858) and semi-quantitative test by Stanley Benedict (1908). Folin in 1919 identified a method for quantitative determination of sugar in blood.

Classification of diabetes mellitus

1. Type-1 Diabetes mellitus (Also known as Insulin-dependent diabetes mellitus; IDDM). About 5% of total diabetic patients are of type-1. Here circulating insulin level is deficient. It is subclassified as
   a. Immune mediated and
   b. Idiopathic
2. Type-2 Diabetes mellitus (Also known as non-insulin dependent diabetes mellitus; NIDDM). Most of the patients belong to this type. Here circulating insulin level is normal or mildly elevated or slightly decreased, depending on the stage of the disease.This type is further classified as:
   a. Obese
   b. Non-obese
   c. Maturity onset diabetes of young (MODY).
3. Diabetic prone states;
   a. Gestational diabetes mellitus (GDM)
   b. Impaired glucose tolerance (IGT)
   c. Impaired fasting glycemia (IFG)
4. Secondary to other known causes
   a. Endocrinopathies (cushings disease, thyrotoxicosis,acromegaly)
   b. Drug-induced (steroids, beta-blockers, etc.)
   c. Pancreatic diseases (chronic pancreatitis, fibro-calculous pancreatitis, hemochromatosis, cystic fibrosis).

Type-1 Diabetes mellitus

1. It is due to decreased production of insulin. Circulating insulin level is low.
2. These patients are dependent on insulin injections. Onset is usually below 30 years of age, most commonly during adolescence. They are more prone to develop ketosis.
3. An autoimmune basis is attributed to most of these cases. Circulating antibodies against insulin is seen in 50% cases and antibodies against islet cell cytoplasmic proteins are seen in 80% cases.

Type-2 Diabetes mellitus

1. 95% of the patients belong to this type. The disease is due to the decreased biologic response to insulin, otherwise called insulin resistance. So there is a relative insulin deficiency.
2. Type-2 Disease is commonly seen in individuals above 40 years. These patients are less prone to develop ketosis.
3. About 60% of patients are obese. These patients have high plasma insulin levels.
4. The maturity Onset Diabetes of Young (MODY) is due to defective glucokinase (GK). This mutation produces relative insulin deficiency by increasing the threshold for glucose-induced insulin secretion.

Regulation of Blood Glucose

The maintenance of glucose level in blood within narrow limits is a very finely and efficiently regulated system. This is important, because it is essential to have a continuous supply of glucose to the brain. Even though it can utilize ketone bodies to some extent, brain has an obligatory requirement for glucose. RBC and renal medulla are also dependant on glucose for meeting their fuel needs.

Factors maintaining blood Sugar

1. The plasma glucose level at an instant depends on the balance between glucose entering and leaving the extracellular fluid.
2. Hormones will make this balance possible.
3. The major factors which cause entry of glucose into blood are:
   a. Absorption from intestines
   b. Glycogenolysis (breakdown of glycogen)
   c. Gluconeogenesis
   d. Hyperglycemic hormones (glucagon, steriods)
4. Factors leading to depletion of glucose in blood are:
   a. Utilization by tissues for energy
   b. Glycogen synthesis
   c. Conversion of glucose into fat (lipogenesis)
   d. Hypoglycemic hormone (insulin)

Postprandial Regulation

Following a meal, glucose is absorbed from the intestine and enters the blood. The rise in the blood glucose level stimulates the secretion of insulin by beta cells of Islets of Langerhan's of the pancreas. The uptake of glucose by most extrahepatic tissues, except brain is dependent on insulin. Moreover, insulin helps in the storage of glucose as glycogen or its conversion to fat

Regulation in Fasting State

1. Normally, 2 to 21/2 hours after a meal, the blood glucose level falls to near fasting levels. It may go down further: but this is prevented by processes that contribute glucose to the blood.
2. For another 3 hours, hepatic glycogenolysis will take care of the blood sugar level.
3. Thereafter, gluconeogenesis will take charge of the situation.
4. Liver is the major organ that supplies the glucose for maintaining blood glucose level.
5. Hormones like glucagon, epinephrine, glucocorticoids, growth hormone, ACTH and thyroxine will keep the blood glucose level from falling. They are referred to as anti-insulin hormones or hyperglycemic hormones.

Metabolic derangements in diabetes

1. Derangements in Carbohydrate Metabolism

Insulin deficiency decreases the uptake of glucose by cells. The insulin dependent enzymes are also less active. Net effect is an inhibition of glycolysis and stimulation of gluconeogenesis leading to hyperglycemia.

2. Derangements in lipid Metabolism

i. Fatty acid breakdown leads to high FFA levels of plasma and consequent fatty liver.
ii. More acetyl-CoA is now available, which cannot be efficiently oxidised by TCA cycle, because the availability of oxaloacetate is limited. The stimulation of gluconeogenesis is responsible for the depletion of oxaloacetate.

iii. The excess of acetyl-CoA therefore is diverted to ketone bodies, leading to ketogenesis. This tendency is more in type-1 disease.
iv. There is hyperlipidemia, especially an increase in NEFA, TAG and cholesterol in plasma.

3. ***Derangements in Protein Metabolism***
Increased breakdown of proteins and amino acids for providing substrates for gluconeogenasis is responsible for muscle wasting.

Causes

Depends on the type of diabetes mellitus

Type-1 diabetes mellitus is partly inherited and triggered by certain infections like Coxsackie B4 virus due to susceptibility of individuals to some of the triggers because of the presence of a genetic element (HLA genotypes).
Type-2 diabetes mellitus is due to life-style and genetic factors.

Complications

Acute complications

1. Diabetic keto-acidosis
2. Hyperosmolar nonketotic coma.

Chronic complications

In 1940 the link is made between diabetes and long term complications.

1. ***Complications in Eyes***
Early development of cataract of lens is due to increased rate of sorbitol formation, caused by hyperglycemia. Retinal microvascular abnormalities lead to retinopathy and blindness.
2. ***Neuropathy***
Peripheral neuropathy with paresthesia is very common. Decreased glucose utilization and its diversion to sorbitol in Schwann cells may be cause for neuropathy. Neuropathy may lead to risk of foot ulcers and gangrene. Hence care of the feet in diabetic patients is important.
3. ***Vascular Diseases***
Atherosclerosis in medium sized vessels, plaque formation and consequent intravascular thrombosis may take place. If it occurs in the cerebral vessels, the result is paralysis. If it is in the coronary artery, myocardial infarction results. In the case of small vessels, the process is called micro-angiopathy, which may lead to diabetic retinopathy, nephropathy and cochleopathy[1,2,3,4,5,6,7]

It is difficult to evaluate the incidence of diabetic complications. Generally diabetics with longer duration will have complications like reinopathy, nephropathy, neuropathy etc. except cochleopathy. Only those diabetics who are not under glycemic control will have hearing loss which is irreversible. Sensori-neural hearing loss affects the inner ear and its central connections leading to functional disability affecting a person's day-to-day activities. This progressive irreversible hearing loss caused by diabetic cochleopathy was proved by many studies. The cause for this diabetic cochleopathy was due to microangiopathy, & neuropathy of the inner ear proved by many studies. Diabetic cochleopathy was correlated with poor glycemic control which was estimated by serum HbA1c levels. Hence diabetic cochleopathy is directly proportional to the elevated glycated HbA1c.

Sensori-neural hearing loss

Results from lesions of the cochlea, VIII nerve or central auditory pathways.

Aetiology of sensori-neural hearing loss

Congenital

Present at birth and is the result of anomalies of the inner ear or damage to the hearing apparatus by prenatal or perinatal factors.

Acquired

Appears late in life. The cause may be genetic or non-genetic. The genetic cause may manifest late (delayed onset) affect only the hearing or a part of a larger syndrome affecting the other systems of the body as well. Common causes of acquired sensori-neural hearing loss include:

1) Infections of labyrinth – viral, bacterial, or spirochaetal.

2) Trauma to labyrinth or VIII nerve, e.g. fractures of temporal bone or concussion of labyrinth or ear surgery.
3) Noise-induced hearing loss.
4) Ototoxic drugs.
5) Presbycusis.
6) Meniere's disease.
7) Acoustic neuroma.
8) Sudden hearing loss.
9) Familial progressive sensori-neural hearing loss.
10) Systemic disorders, e.g. diabetes mellitus, hypothyroidism, kidney disease, auto-immune disorders, multiple sclerosis, blood dyscrasias

Pathophysiology of Diabetic cochleopathy

- Microangiopathy of the inner ear.
- Neuropathy of the cochlear nerve.
- Combination of both.
- Outer hair cell dysfunction
- Disruption of endolymphatic potential.

Microangiopathy of the inner ear

Due to thickening of the basement membranes of capillaries[8,9.] Due to edematous changes of the intermediate cells and atrophy of marginal cells in the stria vascularis. Although angiopathic change occurs as aresult of actiation of polyol pathway in the hyperglycemic state and the stria vascularis is known to be vulnerable to hypoxia, atrophy of stria vascularis may due not only to impairment of blood flow caused by microangiopathy but also to other factors, such as oxidative stress as a result of activation of the polyol pathway in the hyperglycemic state. Diabetic induced apoptotic cell loss may also occur in the diabetic stria vascularis.

Neuropathy of the cochlear nerve

Due to atrophy of spiral ganglion cells. Accumulation of polyols leads to a decrease in myo-inositol and Na+/K+ adenosine tri phosphatase in nerves, contributing to diabetic neuropathy.

Outer hair cell dysfunction [10]

Due to a significant decrease in the number of outer hair cells in the lower and upper turns of cochlea due to observed damage of outer hair cells caused mainly by microangiopathy of the inner ear in cochlear disease in diabetic patients. Other precipating factors such as oxidative stress and apoptosis due to the hyperglycemic state, can work synergistically to cause the observed pathologic changes in the outer hair cells.

Distruption of endolympatic potential

Normal hearing thresholds in our diabetic patients may be related to various factors. Firstly the existence, in the inner ear, of a blood-brain-like barrier (blood-labyrinth barrier), which would maintain the constant composition of endolymph and perilymph (Carlisle et al., 1990; Ito et al., 1993)[11]. Glucose flow from endolymph to perilymph would be regulated by GLUT1 glucose transporters. It is possible that glucose transport in the endolymphatic space is an auto-regulated process protecting the inner ear from hyperglycemia (Ito et al., 1993)[12]. Distruption in this regulation leads to hyperglycemia with hearing loss. Secondly, a role of neurotrophines can be proposed. A reduction of Nerve Growth Factor (NGF) in neuropathic diabetics with limitation of axonal retrograde transport and nervous fibres demyelinization has been reported (Tomlinson et al., 1996)[13]. NGF is a neurotrophic factor essential for survival, development, and maintenance of peripheral and central nervous system. It also exerts neurotrophic and biological activity on non-neural cells (Bonini et al., 1999). A NGF decrease plays an important role in the pathogenesis of diabetic neuropathy (Chiarelli et al., 2000)[14]; Recent data from our group correlate presence of neurosensorial hearing loss with reduction of serum levels of NGF (Salvinelli et al., 2002)[15]; therefore a reduction of NGF may be involved in sensorineural hearing loss in diabetic patients, especially in those suffering from severe diabetic neuropathy.

Diagnosis of diabetic cochleopathy

1. Pure Tone Audiogram [16]

An audiometer is an electronic device that produces pure tones of various frequencies, the intensity of which can be increased or

decreased in 5 decibel steps. Usually air conduction thresholds are measured for tones of 125, 250, 500, 1000, 2000,4000 and 8000 Hertz and bone conduction thresholds measured for 250, 500, 1000, 1500, 2000, 4000Hertz. The intensity that has to be raised above the normal level is a measure of the degree of hearing impairment at that frequency. It is charted in form of a graph called the audiogram. The thresholds of bone conduction are a measure of the cochlear function.

Uses of pure tone audiogram

1) It is a measure of threshold of hearing by air and bone conduction and thus the degree and type of hearing loss.
2) A record can be kept for future reference.
3) Audiogram is essential for prescription of hearing aid.
4) Helps to find degree of handicap for medico-legal purposes.
5) Helps to predict speech reception threshold.

2. Laboratory Investigations in Diabetes

❖ ***Blood glucose level***

For monitoring a diabetic patient, periodic check of fasting and postprandial blood glucose are to be done atleast once in 3 months. Blood glucose level has to be maintained within the normal limits. Persistant hyperglycemia is the most important factor, which leads to chronic complications. Normal levels are: Fasting blood glucose----70to110mg/dl. Sugar estimated in the early morning, before taking any breakfast (12hr fasting) is called fasting blood sugar. (postabsorptive state). Postprandial blood glucose---upto140mg/dl due to prompt secretion of insulin The test done about 2hrs after a good meal is called post-prandial blood sugar (Latin=after food). Random blood glucose---80 to120mg/dl. Blood sugar analysed at any time of the day, without any prior preparations, is called random blood sugar.

❖ ***Sugar in urine***

Normally glucose is not excreted in the urine. But if blood sugar is more than 180mg/dl, urine contains glucose. The blood level of glucose above which glucose is excreted is called renal threshold. Presence of glucose in urine is detected by Benedict's test. It is a semi-quantitative test.

❖ ***Glycated hemoglobin***

The best index of long term control of The blood sugar is measurement of glycated Hemoglobin or glyco-Hb. Non enzymatic addition of any sugar to a protein is called glycation .Glycated Hb refers to glucose derived products of normal adult Hb (HbA).Glycation is a post-translational non – enzymatic addition of sugar residue to aminoacids of protein. When there is hyperglycemia, proteins in the body may undergo glycation. Glucose forms Schiff base with the N-terminal amino group of proteins. When once attached, glucose is not removed from hemoglobin. Therefore it remains inside the erythrocyte, throughout the life span of RBCs (120days). Glycated hemoglobin ais together called HbA1 fraction. Glycated Hb can be separated into HbA1a, HbA1b, HbA1c. Due to electrophoretic behaviour of these minor Hb they are referred to fast Hb. Glycated Hb is generally called as HbA1 fraction consisting of a total of 574 aminoacids. [α-141 aminoacids, β-146aminoacids] Out of this 80% molecules are HbA1c, where glucose is attached to the N-terminal valine of β chain of hemoglobin. HbA1c measures the number of glucose molecules attached to hemoglobin, a substance in red blood cells. People who don't have diabetes mellitus generally have an HbA1c level of less than 6%. i.e. less than 6% of their hemoglobin molecules have glucose permanently attached. Hemoglobin is the oxygen carrying pigment which gives blood its red color and also which is the predominant protein in red blood cells. About 90% of hemoglobin is hemoglobin A. (The "A" stands for adult type.) Although one chemical component accounts for 92% of hemoglobin A approximately 8% of hemoglobin A is made up of minor components that are chemically slightly different. These minor components include hemoglobin A1c, A1a1, A1a2 and A1b. Hemoglobin A1c (HbA1c) is a minor component of hemoglobin to which glucose is bound.HbA1c is also referred to as glycosylated or glucosylated hemoglobin.

Besides adult Hb other minor Hb as

Minor Hb	Components	% of total Hb
1)HbA1	α2β2	90%
2)HbA2	α2δ2	<5%
3)HbF	α2γ2	<2%
4)HbA1c	α2β2-glucose	<5%

According to the Diabetes Control and Complications Trial (DCCT), tight glycemic control could reduce the risk of diabetic eye, ear, kidney and nerve disease, so the American Diabetes Association (ADA) recommends that people with diabetes try to keep their HbA1c level below 7%. A general range for HbA1c levels is

Healthy HbA1c level----Less than or equal to 6%.

Good control of diabetes mellitus---- 6% to 7%.

Poor control of diabetes mellitus----- above 7%.

Interpretation of Glycated Hemoglobin

Determination of glycated hemoglobin is for monitoring the response to treatment, not for diagnosis of diabetes mellitus. The rate of synthesis of HbA1c is directly related to the exposure of RBC to glucose. Thus the concentration of HbA1c is an indication of the blood glucose concentration over the previous 10-12 weeks. It is unaffected by recent food intake or recent changes in blood sugar levels. An elevated glycated hemoglobin indicates poor control of diabetes mellitus. The risk of cochleopathy is proportionately increased with elevated glycated hemoglobin value [7]. Reduction in 1% glycated hemoglobin will decrease long term complication to an extent of 30%. Glycated protein mediate some of the early microvascular changes of diabetes.

A major study published in 2000, (UKPDS Study) quantified many of the benefits of reducing a high HbA1c level by just 1%.[17]

1. A 43% decrease in risk of amputation
2. A 37% decrease in risk of small vessel disease (inner ear vessels damage causing cochleopathy).
3. A 21% decrease in risk of diabetes-related death.
4. A 16% decrease in risk of heart failure.
5. A14% decrease in risk of fatal or non fatal myocardial infarction (heart attack).
6. A 12% decrease in risk of fatal or non fatal stroke.

Estimation should be done at least every 3 months in all patients on treatment. Glycated hemoglobin <7% indicates adequate control of diabetic state[18]. Periodic monitoring of HbA1c levels document the degree of control of glucose in diabetic patients and development of sequalae can be assessed[19,20].

CONCLUSION

It is concluded that diabetes may be one of the causative factor for cochleopathy particularly those patients not under glycemic controlwhich can be assessed by estimating HbA_{1c}, the diagnostic tool for control of glycemia. So it is advisable to screen the diabetics with pure tone audiogram and to check the glycemic status by estimating HbA_{1c} at least once in 3 months.as suggested.

REFERENCES

1. Friedman SA, Schulman RH, Weiss S. Hearing and diabetic neuropathy. Arch Intern Med. 1975; 135:573–6.
2. Kakarlapudi V, Sawyer R, Staecker H. The effect of diabetes on sensorineural hearing loss. Otol Neurotol. 2003; 24:382–6.
3. Kurien M, Thomas K, Bhanu TS. Hearing thresholds in patients with diabetes mellitus. J Laryngol Otol. 1989; 103:164–8.
4. Dalton SD, Cruickshanks KJ, Klein R, Klein BE, Wiley TL. Association of NIDDM and hearing loss. Diabetes Care. 1998; 21:1540–4.
5. Cullen JR, Cinnamond MJ. Hearing loss in diabetics. J Laryngol Otol 107:179-82, 1993.
6. Tay HL, Ray N, Ohri R, Frootko NJ. Diabetes mellitus and hearing loss. Clin Otolaryngol 20:130-4, 1995.

7. Jordao A.Consideration Sur un cas du diabete Union Medicale du Paris 1857; 11: 446.
8. Smith TL, Raynor E, PrazmaJ, Buenting JE, Pillsbury HC. Insulin dependent diabetic microangiopathy in the inner ear. Laryngoscope. 1995; 105; 236-240.
9. Makishima K, Tanaka K. Pathological changes of the inner ear and central auditory pathway in diabetics. Ann Otol Rhinol Laryngol. 1971; 80: 218-228.
10. Suckfull M, Winkler G, Trein E, Raab S, Schorl K, Mees K. Changes in serum osmolarity influence the function of outer hair cells. Acta Otolarngol. 1999; 119:316–21.
11. Carlisle L, Steel K, Forge A. Endocochlear potential generation is associated with intercellular communication in the stria vascularis: structural analysis in the viable dominant spotting mouse mutant. Cell Tissue Res. 262:329-37, 1990.
12. Ito, Samuel S. Spicer and Bradley A. Schulte. Immunoistochemical localization of brain type glucose transporter in mammalian inner ear: Comparison of developmental and adult stages. Hearin research 71: 230-238, 1993.
13. Tomlinson DR, Femyhough P, Diemel LT, Maeda K. Deficient neurotrophic support in aetiology of diabetic neuropathy. Diabet Med 13:679-81, 1996.
14. Chiarelli F, Santilli F, Mohn A. Role of growth factors in the development of diabetic complications. Horm Res.53 (2):53-67, 2000.
15. Salvenelli F, Miele A, Casale M, Greco F, D'Ascanio L, Firrisi L, et al. Hearing thresholds in patients with diabetes. Int J Otorhinolaryngol 2004.
16. Kerr AG, Stephans D. Scott- Brown's Otolaryngology: Adult Audiology. 6th ed. Volume 2. Butterworth Heinemann; 1997. pp. 2/1/6–9.
17. Koenig RJ, Peterson CM, Jones RL, Sandek C, Lehrman M, Cerami A.Correlation of glucose regulation and hemoglobin A1c in diabetes mellitus.1976.
18. Sumathi.K.,Prakash.M.etal. Significance of HbA1c in deafness in type-2 diabetes mellitus. Pharm Biomed Sci.2012, November, 24(24);59-61.
19. Somogyi A, Rosta K, Vaszi T. Hearing impairment and tinnitus in patients with type 2 diabetes 2013, Mar 10;154(10):363-8.
20. Sayyed Ahmadreza Okhovat, Mohammad Hassan Moaddab, [...], and Zahra Abdeyazdan Evaluation of hearing loss in juvenile insulin dependent patients with diabetes mellitus. J Res Med Sci.2011,February, 18(2):179-183.