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DEVELOPMENT OF DIABETES MELLITUS, G-6-P-D DEFICIENCY IS A POTENTIAL RISK FACTOR

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Abstract

Glucose-6-phosphate dehydrogenase is an enzyme present in most human tissue, which is involve in the production of reduced glutathione (GSH) from oxidized glutathione (GSSH) in the hexose mono phosphate shunt (HMP shunt). The reduced glutathione (GSH) is a key product in the control of oxidative stress. If the activity of G-6-P-D defect by every reasons in the cells will lead to G-6-P-D deficiency. The deficiency of G-6-P-D is increased the level of oxidative stress which is causes diabetes mellitus type 2. It means that the G-6-P-D deficiency is one of the risk factor for development of diabetes mellitus type 2. So, diabetes mellitus type 2 is one of the life treating disease in many populations. The G-6-P-D deficiency is an X-linked hereditary disorder which is more common in men among the African countries. In this study I select one of the African countries "Ghana; west of Africa" which studied in the Centeral Regional Hospital located in Cape Coast in the central Region of Ghana. The prevalence of G-6-P-D deficiency studied by M.B Adinortey, R.K Owusu, I.K. A. Galyuon, W.Ekloh, I. Owusu and D.A. Larbi. The prevalence of G-6-P-D deficiency whichdeveloped the diabetes mellitus type 2 studied among the 422 participants (diabetic and non-diabetic participants). The prevalence G-6-P-D deficiency is more common in diabetic patients as compare as the non- diabetic participants. The treatment or prevention of G-6-P-D deficiency decreases the level of diabetic mellitus type 2 development.

KEYWORDS: G-6-P-D deficiency, diabetes mellitus type 2, oxidative stress, African countries.

Introduction

HMP shunt: Hexose monophosphate pathway or HMP Shunt is also called pentose phosphate pathway or phosphogluconate pathway. This is an alternative pathway to glycolysis and TCA cycle for the oxidation of glucose. However, HPM shunt is more anabolic in nature, since it is concerned with the biosynthesis of NADPH and pentose. The sequence of

reactions of HMP shunt is divided into two phases-Oxidative and Non oxidative phases.

In oxidative phase Glucose 6- phosphate dehydrogenase (G-6-P-D) is a dependent enzyme that converts glucose 6-phosphate to 6-phosphogluconolactone. The latter is then hydrolyzed by the gluconolactone hydrolase to 6-phosphogluconate. The next reaction involving the synthesis o NADPH is catalyzed by 6-phosphogluconate dehydrogenase to produce 3 keto 6-phosphogluconate which then undergoes decarboxylation to give ribulose 5 phosphate. In the Non oxidative reactions are concerned with the interconversion of three, four, five and seven carbon monosaccharides.

Significance of HMP shunt: HMP shunt is unique in generating two important products- Pentose and NADPH needed for the biosynthetic reactions and other functions. The most important pentose which is produce in HMP shunt is ribose 5- phosphate. This pentose or its derivatives are useful for the synthesis of nucleic acid and many nucleotides. In the other hand importance of NADPH; there is a continuous production of H_2O_2 in the living cells which can chemically damage unsaturated lipids, proteins and DNA.This is, however, prevented to a large extent through antioxidant (free radical scavenging) reactions involving NADPH. Glutathione mediated reduction of H_2O_2 is given in the (**figure1**). Glutathione (reduced, GSH) detoxifies H_2O_2, peroxidase catalysis this reaction. NADPH is responsible for the regeneration of reduced glutathione from the oxidized one. As well as the NDPH is involving in amino acids synthesis, fatty acid biosynthesis, detoxification of drugs, phagocytosis and special function of NADPH is in RBC which preserve the integrity of RBC membrane(Satyanarayana*et. Al.*, 2013).

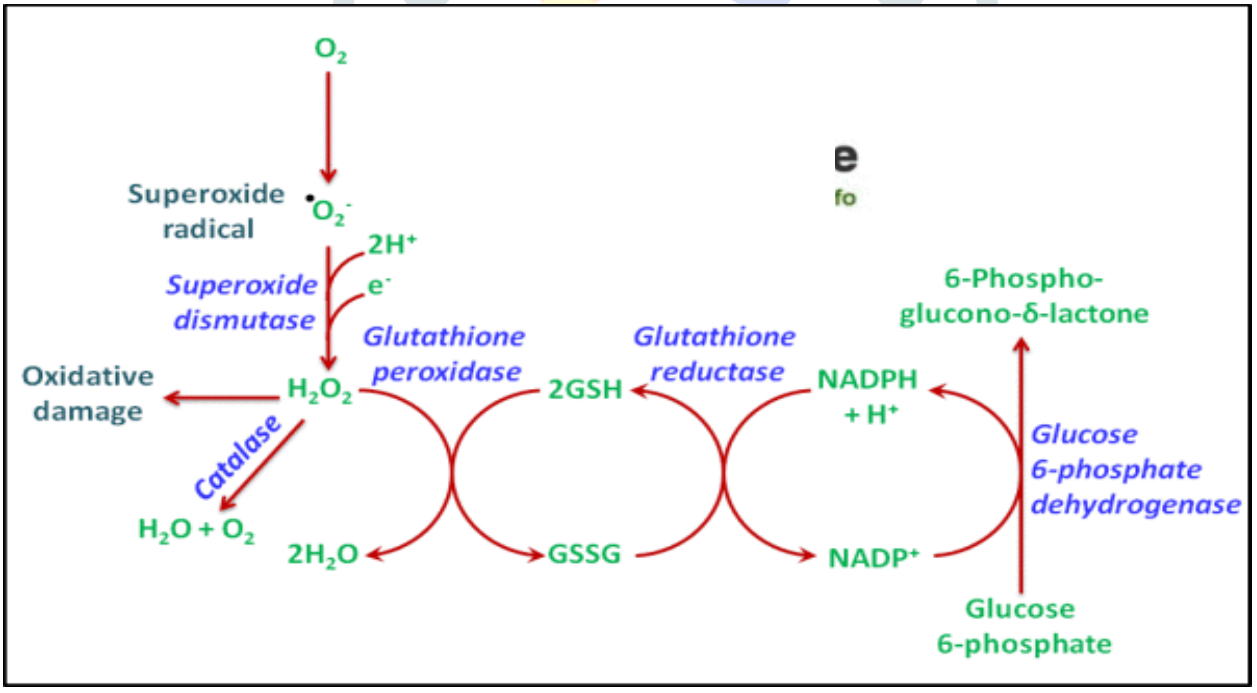

Figure 1: Role of NADPH and Glutathione in preventing oxidative damage in cells.

Glucose 6- phosphate dehydrogenase deficiency (G-6-P-D deficiency): G-6-PD deficiency is the most usual enzymopathies disorder in human which affecting about 400 million people in the world. G-6-P-D deficiency is an X-linked disorder that causes by mutation in G-6-P-D gene, which is a hereditary genetic defect(Adinorteye*t. Al.*, 2011). As the gene determining the structure G-6-P-D is on the X chromosome, inheritance is sex-linked with men expressing the full defect (Cappai.

et.,al. 2011). Mutation in the G-6-P-D gene result in protein variants with different levels of enzyme activity, accounting for a wide spectrum of biochemical and clinical phenotypes(Carette. *et., al.2010*).

The progression of G-6-P-D deficiency could worsen, but also attenuate, the all process leading to diabetes. As I mentioned, NADPH is for regenerate GSH (reduced glutathione), and the deficiency of G-6-P-D facilate the production of oxidative stress (Cappai. *et.,al. 2011*). The most clinical importance of G-6-P-D deficiency is hemolytic anaemia, because the HMP shunt generate the NADPH which are protected the RBC from the oxidation in the presence of drugs,infections, and fava beans consumptions(Satyanarayana*et. Al.*, 2013). As well as the NADPH is working as cofactor for endothelial nitric oxide synthase, whenever the G-6-P-D deficiency is occur the NADPH generating stop and diabetic vascular disease by magnifying endothelial dysfunctions.

There are some previous reported in different regions of the world(specially African countries; Ghana;) has shown that high level of glycosylated hemoglobin and decrease level of GSH(reduced glutathione) in the blood of those who has G-6-P-D deficiency subjects compared to normal cases. The deficiency of G-6-P-D increased the generation of oxidative stress in their cell due to major biochemical dysfunction of G-6-P-D enzyme. The G-6-P-D enzyme is responsible to generate NADPH which is necessary for reducing of GSSH (oxidized glutathione) to GSH (reduced glutathione) that involve in protection of cells against the free radicals attack(Adinorteye*t. Al.*, 2011).

Free radical (oxidative stress), which are generating in G-6-P-D deficient subject is reported the individual subject to diabetes mellitus (Pradeep. *et., al. 2016*). It shows that one of the factor which is involve in the pathogenesis of diabetes mellitus is G-6-P-D deficiency. According to study in different region by the researchers, glucose level is altered in G-6-P-D deficiency cases. As well as the report in this paper shows that the level of GSH in blood of diabetic cases is decreased. These studies suggest that the G-6-P-D deficient cases may be more sensitive to diabetes mellitus than the non- G-6-P-D deficient cases.

Based on this paper, it suggested that there is an association between the diabetes mellitus and G-6-P-D deficiency cases and this deficiency is one of the most important risk factor for increase the level of glucose which known as diabetes mellitus. The risk factor for diabetes mellitus is high level of oxidative stress or free radical which is generating by G-6-P-D deficient cases. From this point, the main aim of this paper is to evaluate the association between the G-6-P-D deficiency and diabetes mellitus cases.

Materials and Methods

Study area

According to the prevalence of G-6-P-D deficiency which is more common in African countries (Satyanarayana. *et., al.2013*), I selected Ghana, which is located at the west of Africa. The study was done in the Central Region of Ghana within December 2009 –May 2010. All participants were divided in two groups, one group which every individual had diabetes mellitus and other group which didn't has diabetes mellitus. The non-diabetic persons controlled via world health organization (WHO, 2006) standards. All the participants were fully examined at Central Regional hospital of Ghana by Doctors. They were selected randomly. In totally 422 individual participate and enrolled for study, the half of the participants are diabetes mellitus positive and half of the participants were non-diabetics. The patients which diabetes were positive,they were all according to the diagnosis by Central Regional

Hospital and the participants which non-diabetic from the Cape Coast metropolis of Ghana. The participant who were suffering from Sickle cell anaemia were excluded from this study, because the sickle cell anaemia also associated with free radicals and insulin resistance. According to WHO,diabetic's patients had (FBG≥7.0mmol/L) and non-diabetics participants had (FBG≤6.7mmol/L) (WHO 2006). All data analyzed statistically by using SPSS version 16.0 and commonly saved in a database.

Results

The age of all participants were from 17 to 81 years which the median age were 43 years. As well as the diabetics patients had higher BMI than the non-diabetic participants and the level of fasting blood glucose (FBG) were higher than the non-diabetic participants.

Among the 211 diabetic patients included in this study, there was higher prevalence of G-6-P-D severely defective (35.1%) as compared to 12.8% of 211 non-diabetic participants. And also there was higher prevalence of G-6-P-D non-defective (77.7%) in non-diabetic participants as compare to 49.3% of diabetic patients. In the moderate defect of G-6-P-D the prevalence was 15.6% for diabetic patients as compare to non-diabetic participants which was 9.5% (Adinorteyet. *Al.*, 2011).

Discussion

Diabetes mellitus is a disease which causes by many factors, one of the factors which involve in diabetes mellitus is high level of oxidative stress. The factor which increased the level of oxidative stress is deficiency of G-6-P-D, in this case the deficiency of G-6-P-D is well known risk factor for diabetes mellitus.Diabetes mellitus is the life treating for most countries. In this research the level of glucose in blood is indicated by fasting blood glucose (FBG) for diabetic and non-diabetic participants. Also the other factor which studied in this research was Body Mass Index (BMI), because BMI is one of the most important risk factor for diabetes mellitus .As well as the age of participants studied in this research (Adinorteyet. *Al.*, 2011).

From several articles paper it was clear that there were different level of association between the G-6-P-D deficiency and diabetes mellitus. This cases and the other reported by many article papers reported that there were higher prevalence of G-6-P-D deficiency in diabetes mellitus type 2 than in the non-diabetics person (2),(3),(4),(5).

There are many reasons which show that G-6-P-D deficiency is one of the risk factor for diabetes mellitus. In the deficiency of G-6-P-D, pentose phosphate pathway is unable to generate enough amount of nicotine amide adenine dinucleotide phosphate (NADPH) to convert the GSSH (oxidized glutathione) to GSH(reduced glutathione), which the decreased level of GSH is responsible for increase the level of oxidative stress and increase the development of diabetes mellitus (Adinortey.*et., al.2011).*

Beta cells in islets Langerhans of pancreases is the place for synthesis of insulin which decrease the level of glucose in the blood are easily sensitive to the high level of oxidative stress (reactive oxygen species) and easily can destroy by these free radicals. The factors which is responsible for generating of reactive oxygen species is the deficiency of G-6-P-D (Adinortey.*et. al. 2011).* Diabetes mellitus also inhibit the G-6-P-D enzyme by the activation of protein kinase A (PKA), which involve in the production of oxidative stress and free radical in the rat kidney cortex (Yizhen Xu.*et., al. 2005).* Thesereasons and finding indicate the developing of diabetes mellitus type 2 by G-6-

P-D deficiency patients. Not only diabetes mellitus but also other oxidative stress –related disease such as cancer are associated with the deficiency of G-6-P-D. According to these reasons the increase activity of G-6-P-D enzyme will prevent the beta cell of Langerhans of pancreases from death. All these reasons confirm the importance of G-6-P-D deficiency in the development of diabetes mellitus type 2 as studied at Central Regional hospital of Ghana.

There is a limitation in this study which indicate that the G-6-P-D deficiency is not the causative agents that causes the diabetes mellitus, but it is one of the risk factors for development of diabetes mellitus. Also for confirmation of oxidative stress presence in G-6-P-D deficiency can easily be shown by measuring some oxidative stress indicators. For better studying it is required to study deeply by molecular biology tools to prove the G-6-P-D deficiency as a risk factor for diabetes mellitus (Adinortey.*et.,al. 2011*).

Conclusion

G-6-P-D deficiency affect about 400 million people in the world. Diabetes mellitus is more common in African country who are affected by G-6-P-D deficiency. (Carette.*et, al. 2010*). The result of this study suggested that the deficiency of G-6-P-D is one of the risk factors for diabetes mellitus development. By finding out some development in the treating of the G-6-P-D deficiency by some studying in the future, the risk of diabetes mellitus will be reduce. As well as if the level of G-6-P-D determine by screening test, this will be identify the diabetes mellitus and also will help in the prevention of diabetes mellitus type 2 (adinortey.*et., al.2011*).

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