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REVIEW

Distribution of genetic polymorphism of the *PTP1B* gene in diabetes mellitus patients taking insulin therapy in Indonesia: A narrative review

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Abstract

Background: Diabetes mellitus is a metabolic disease directly related to the onset of hyperglycemia, which occurs due to abnormalities in insulin secretion, insulin action, or both. Protein Tyrosine Phosphatase 1B (PTP1B) from insulin receptor signal transduction has a role in the pathogenesis of diabetes mellitus. **Objective:** To briefly present the distribution of genetic polymorphism of the PTP1B gene in diabetes mellitus patients taking insulin therapy. **Method:** A narrative review was done by collecting scientific journals from several leading platforms, such as PubMed, CrossRef, and Google Scholar, in the English language, published from 2012 to 2023. **Result:** PTP1B can inhibit glucose transporter type 4 (GLUT4) activation in glucose uptake by cells, increasing glucose levels. The use of exogenous insulin becomes ineffective, and insulin resistance occurs. This study has limitations and needs additional prospective investigations to corroborate the findings. **Conclusion:** In some studies, PTP1B gene polymorphism in diabetes mellitus patients strongly correlates with insulin therapy. PTP1B gene polymorphism can cause insulin resistance because PTP1B and GLUT4 have the opposite effect.

Introduction

Diabetes mellitus is a group of chronic metabolic diseases characterised by hyperglycemia, consistent with abnormalities in insulin secretion, insulin action, or both. To prevent chronic complications and lower the risk of long-term complications, diabetes mellitus must be treated using independent treatment training and medical science (American Diabetes Association, 2016). Intensive cell sensitivity to insulin causes hyperglycemia. The cause of people suffering from type 2 diabetes mellitus is an unhealthy lifestyle and unhealthy eating patterns. Diabetes mellitus sufferers occur in people who are overweight, have minimal physical activity and are ageing (Sun *et al.,* 2016; Sorli, 2014). Type 2 diabetes mellitus causes glucose to accumulate in the blood vessels and causes an increase in blood sugar. At the same time, insulin target cells experience a decrease in the amount of glucose, thereby disrupting cell performance and function (Mackawy, 2017).

The International Diabetes Federation (IDF) reports that the number of people suffering from diabetes mellitus globally will increase to 537 million people in 2021, and the number of deaths in this case is 6.7 million people (Figure 1). Additionally, the IDF predicts that the number of people with diabetes mellitus will rise from 10.7 million in 2019 to 13.7 million in 2030 (International Diabetes Federation, 2021). The World Health Organisation (WHO) projects that by 2030, 21.3 million people in Indonesia will have type 2 diabetes mellitus, up from 8.4 million in 2000 (Cederberg & Laakso, 2014). Indonesia is fifth, with a total of 19.47 million sufferers. Riset Kesehatan Dasar (RISKESDAS) shows that the prevalence of diabetes mellitus in Indonesia is 2% in people aged ≥ 15 years. DKI Jakarta Province has the highest prevalence rate in Indonesia,

with an incidence percentage of 3.4% of the total 10.5 million people or the equivalent of 250 thousand people in DKI Jakarta suffering from diabetes mellitus (Kemenkes RI, 2018).

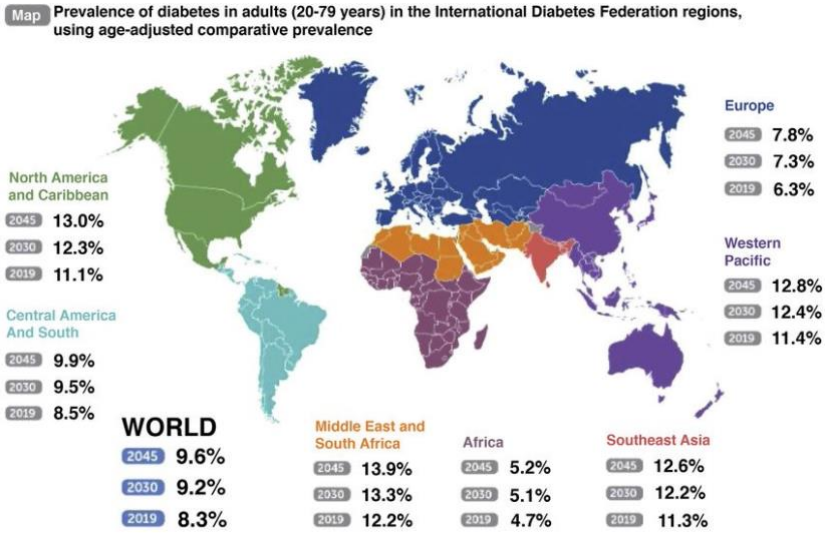

Figure 1: The prevalence of diabetes among adults (20-79 years) in the IDF areas

Protein tyrosine phosphatase 1B (PTP1B) is a protein causative factor for diabetes mellitus (Sun *et al.,* 2016). PTP1B from insulin receptor signal transduction that has a role in the pathogenesis of diabetes mellitus. People with type 2 diabetes mellitus certainly have different genetic variations, so it is necessary to carry out pharmacogenetic studies to solve the problem. One of the genetic variations in cases of diabetes mellitus 2 is the variation in the PTP1B gene when carrying out gene expression (Sun *et al.,* 2016).

The polymorphism activity of the PTP1B gene can identify specific therapies for people with different genetic structures. PTP1B gene activity can be identified by observing the distribution of gene polymorphisms (Priefer, 2020). The PCR-RFLP method is the most effective method by recognising and cutting (destroying) DNA molecules at certain locations, called recognition sites or cutting sites (Tsou & Bence, 2022). A simple analysis of the distribution of *PTP1B* gene polymorphism can be observed by calculating the length of movement of DNA fragments in gel electrophoresis. The difference in the size of DNA fragment movement with the specific type of control used will indicate the distribution of PTP1B gene polymorphism (Mackawy, 2017).

This article briefly presents the distribution of genetic polymorphism of the PTP1B gene in diabetes mellitus patients taking insulin therapy in Indonesia.

Methods

The authors have searched PubMed, CrossRef, and Google Scholar using a combination of the following terms: "*diabetes mellitus*", "*insulin therapy*", "*polymorphism*", "*PTP1B*", and "*genetic*" to retrieve all articles related to the correlation with the study objectives and scientific relevance of a possible link between the distribution of genetic polymorphism of the *PTP1B* gene and diabetes mellitus, which obtained from 2012 to 2023, and in the English language.

Results and Discussion

The pancreatic B cells that produce insulin are peptide hormones with an anabolic effect. It exerts its pleiotropic effects by binding to receptors on target organs like the liver, skeletal muscle, fat, and others (Gupta, 2012; Nassel & Broeck, 2016; Komatsu *et al.,* 2019). It encourages glucose storage into glycogen in the liver, reduces glucose output, and activates GLUT4 translocation in fat to improve glucose transport (Leto & Saltiel, 2012).

Increased PTP1B activity is caused by insulin resistance factors, which stimulate the occurrence of type 2 diabetes mellitus (Ali *et al.,* 2017). In type 2 diabetes patients affected by insulin resistance, the insulin signalling pathway does not function properly, which can affect GLUT4 activity. PTP1B, an inhibitor of insulin signalling, may contribute to insulin resistance by reducing the activation of the insulin signalling pathway

(Jiang *et al.,* 2012). When PTP1B is overactive, it can inhibit GLUT4 activation and glucose uptake by cells, leading to increased blood glucose levels (Rocha *et al.,* 2022) (Figure 2).

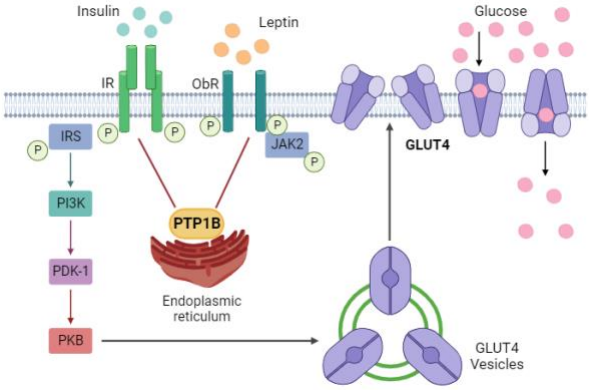

Figure 2: Schematic representation of the negative regulation by *PTP1B*.

PTP1B negatively regulates the signalling of leptin and insulin. PTP1B works in the insulin signalling pathway by dephosphorylating the insulin receptor substrate (IRS) or active insulin receptor (IR) (Liu *et al.,* 2022). In cell culture, overexpressing PTP1B can decrease the phosphorylation of IR and/or IRS-1 in response to insulin stimulation, whereas underexpressing PTP1B can improve insulin-stimulated signalling (Jiang *et al.,* 2012). The insulin signal transduction pathway is mediated by the insulin receptor (IR) on the cell membrane (Choi *et al.,* 2016; Deshmukh, 2016). Depending on whether the IRS (insulin receptor substrate) is mediated, IR-mediated signal transduction pathways can be classified as IRS-mediated signal transduction pathways and non-IRS-mediated signal transduction pathways (Minard *et al.,* 2016). By progressively phosphorylating the insulin-bound insulin receptor (IR), insulin receptor substrate (IRS), and glucose transporter type 4 (GLUT4), the insulin signal cascade causes glucose uptake through the translocation of GLUT4 (Minard *et al.,* 2016).

The polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) approach depends on the digestion of PCR amplicons with the appropriate restriction enzymes to produce various polymorphic fragments that may be utilised as markers for species identification (Kim, 2017). PCR-RFLP is also known as a cleaved amplified polymorphic sequence. This technique involves treating a PCR amplicon with a particular restriction endonuclease (RE), which causes the DNA to be cut at a particular restriction site called the recognition site, resulting in many DNA fragments of various sizes. The digested amplicons are subjected to an electric field while supported on a gel. The bands will move across the gel at varying rates and sizes. The two main limitations of PCR-RFLP are the requirement for specialist RE and the difficulty of identifying the particular variation when several single nucleotide polymorphisms (SNPs) are being targeted simultaneously. However, mixing two enzymes in a single reaction can substantially alleviate this issue (Tarhan *et al.,* 2017; Zhang *et al.,* 2013) (Figure 3).

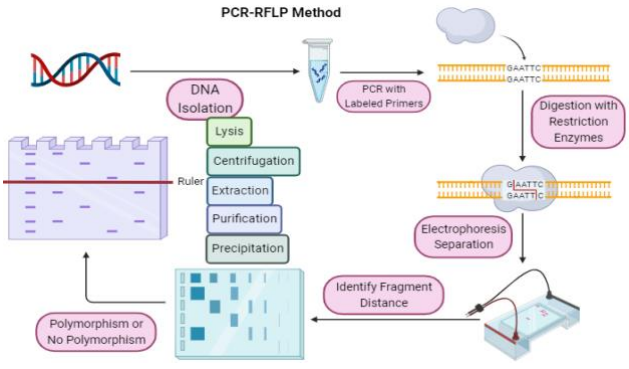

Figure 3: Schematic representation of PCR-RFLP method and fragment length analysis in gel electrophoresis

PCR-RFLP can detect genetic polymorphisms in DNA by combining PCR to amplify certain DNA sequences and RFLP to analyse polymorphisms based on restriction enzyme cutting (Fernando *et al.,* 2018). Polymorphism distribution can be measured by calculating the length of movement of DNA fragments in gel electrophoresis using a ruler (Perry *et al.,* 2012). The difference in the size of DNA fragment movement with the specific type control used will indicate the distribution of PTP1B gene polymorphism (Pouryasin *et al.,* 2017; Hashim *et al.,* 2019) (Table I).

Table I: Research study on the distribution of PTP1B gene polymorphism

Research title	Research subject	Result	Researcher	Year
Association of protein tyrosine phosphatase 1B gene polymorphism with the effects of weight reduction therapy on bodyweight and glycolipid profiles in obese patients	Prospective cohort study Number of subjects: 447 obese and overweight outpatients Location: Japan	Patients with the T allele at SNP rs3787348 PTPN1 experienced significantly smaller reductions in BMI, body weight, and waist circumference during weight loss therapy.	Hajime Yamakage, Yousuke Konishi, Kazuya Muranaka, Kikuko Hotta, Yoshihiro Miyamoto, Hiroko Morisaki, Takayuki Morisaki, Noriko Satoh-Asahara (Yamakage *et al.,* 2021)	2021
Scanning SNPs of Diabetes Mellitus related gen*es; HNF4A, PTPN, KCNJ11, PPAR gamma; among Thalassemia* Patients: a Preliminary Study	Cross sectional study Number of subjects: 100 thalassemia patients using PCR-RFLP Location: Indonesia	The *PTPN* gene from 467 T > C has a CC percentage of 90%, CT 10%, and MAF 5%.	L Rujito, F Fauziyah, E F Azizah, Q Santosa, A T Hapsari, D U Anjarwati, F Arjadi (Rujito *et al.,* 2019)	2019
Protein Tyrosine Phosphatase 1B (PTPN1) Gene polymorphism (467T > C) and Metabolic Syndrome: A Pilot Study	Case control study Number of subjects: 180 patients using PCR-RFLP Location: Egypt	467T>C PTPN1 variant showed no significant correlation with metabolic syndrome.	Amal MH Mackawy (Mackawy, 2017)	2017
The Role of Polymorphism Gly972Arg IRS-1 Gene and C981T *PTP-1B* Gene on Insulin Resistance Young Adult Subjects with low birth weight History	Retrospective cohort study Number of subjects: 97 low birth weight baby subjects and 100 normal birth weight baby subjects using PCR-RFLP Location: Indonesia	Metabolic dysfunction in normal birth weight baby subjects with the Cys981Tyr polymorphism of the PTPN1 gene increased diastolic blood pressure, namely 1.11 times compared to the normal birth weight baby subjects with the natural PTPN1 gene, whereas in the low birth weight baby subjects there was no difference between the PTPN1 genotypes.	Hikmat Permana, Gaga Irawan Nugraha, Sri Hartini K. S. Kariadi (Permana *et al.*, 2012)	2012

Conclusion

Numerous studies have shown compelling evidence of a correlation between the PTP1B polymorphism and the utilisation of insulin therapy among diabetes mellitus patients. In many scholarly publications, PTP1B regulates protein tyrosine phosphorylation levels in both healthy and unhealthy settings, and it has both favourable and unfavourable impacts on cellular signal transmission. Moreover, it has been observed that the PTP1B gene, specifically in individuals with the CC and CT allele, has a significant correlation with an elevated susceptibility to diabetes mellitus. PTP1B functions to inhibit the leptin and insulin signalling pathways.

The distribution *of PTP1B* polymorphisms can help identify and find solutions regarding the effective use of insulin for diabetes mellitus patients. By minimising their opposing effects, researchers can modify the activities of PTP1B and GLUT4 and develop novel therapeutic targets to treat insulin resistance and diabetes mellitus. Additional research is required to ascertain an association between these variables in larger and more comprehensive sample sizes. The present study demonstrates various limitations and calls for further prospective investigations to validate the results.

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