



Role of FNDC5 gene polymorphism in patients with diabetic nephropathy

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Abstract:

A category of metabolic illnesses known as diabetes mellitus (DM) is characterized by levels of hyperglycemia that persist for an extended length of time. The primary underlying cause of Type 2 diabetes mellitus (DM) is insulin resistance, which may also be accompanied by substantially decreased insulin production. The long-term presence of hyperglycemia causes several problems, including diabetic nephropathy. White adipose tissue (WAT) and brown adipose tissue (BAT) are the two separate compartments that make up adipose tissue. BAT has a thermogenic activity and controls body temperature by dissipating energy through heat generation. It is believed that the browning of adipose tissue will increase insulin sensitivity and lessen weight gain. Muscle-adipose tissue cross-talk may be facilitated by irisin, a newly identified exercise-mediated myokine that controls energy metabolism by transforming white into brown fat. When the precursor plasma membrane protein fibronectin type III domain-containing protein 5 (FNDC5) is broken down, irisin is created and released into the bloodstream. In individuals with diabetic nephropathy and chronic kidney disease (CKD), irisin was discovered to be related to renal functioning. To identify variations in the incidence of diabetic nephropathy among diabetic patients, the role of FNDC5 genetic polymorphism and irisin expression in T2DM nephropathy is being studied

Keywords: FNDC5, Gene polymorphism, Diabetic nephropathy, Irisin, type 2 diabetes mellitus.

Introduction:

The most prevalent endocrine metabolic illness is diabetes mellitus, which affects 170 million people globally ⁽¹⁾. It stands for a set of illnesses with complicated, varied etiologies that are characterized by chronic hyperglycemia and aberrant protein, fat, and carbohydrate metabolism brought on by insulin insufficiency or resistance ⁽²⁾. Diabetes mellitus is categorized as Type 1 Diabetes, Type 2 Diabetes, other

Specified sorts of Diabetes, and Gestational Diabetes (GDM) ⁽³⁾.

Type 2 diabetes mellitus:

Type 2 diabetes mellitus (T2DM), which is due to either decrease insulin production, insulin resistance, or both which shows disruption of protein, lipid, and carbohydrate metabolism. T2DM is the most prevalent kind of diabetes, making up more than 90% of all cases, compared to the other two ⁽⁴⁾. T2DM has a complex pathophysiology that includes

both hereditary and environmental components. The pathophysiological changes include chronic inflammation, insulin resistance, and β -cell dysfunction, all of which gradually impair blood glucose regulation and cause the emergence of microvascular and macrovascular problems⁽⁵⁾. Insulin resistance is brought on by being overweight, sedentary behavior, and a hereditary susceptibility⁽⁶⁾, which place stress on β -cells, resulting in a breakdown of cell function and a gradual decrease in the production of insulin⁽⁷⁾. Patients with diabetes mellitus who have diabetic nephropathy (DN), commonly referred to as diabetic kidney disease, continuously lose kidney function.⁽⁸⁾ The prevalence of DN has been rising globally, and 20% of type 2 diabetes patients are predicted to have end-stage renal disease (ESRD) throughout their lifetimes⁽⁹⁾. Diabetic nephropathy is the most common cause of end-stage kidney disease, which may require a kidney transplant or hemodialysis. It is linked to a higher chance of dying overall, especially from cardiovascular disease⁽¹⁰⁾.

Components of adipose tissue:

Brown and white adipocytes are the two main forms of adipocytes seen in mammals. White adipocytes are in charge of energy storage, but brown adipocytes express uncoupling protein 1 (UCP1), which is required for non-shivering thermogenesis.⁽¹¹⁾ Uncoupling protein 1 (UCP1), without ATP synthesis, can pass protons across the inner mitochondrial membrane, releasing energy as heat instead⁽¹²⁾. Using UCP1 as a target will help fight diabetes, reduce body fat, and enhance overall metabolism.⁽¹³⁾ Consequently, converting fatty tissue from white to brown is thought to improve insulin

sensitivity and lessen the increase in weight⁽¹⁴⁾.

Irisin a novel myokine:

Irisin is a myokine that is activated by exercise and regulates energy metabolism by converting white fatty tissue into brown fatty tissue, and it may participate in the interaction between fatty tissues and muscles⁽¹⁵⁾. Irisin is a hormone-like polypeptide of 112 amino acids that is created by cleaving the precursor plasma membrane protein of (FNDC5) and is released into the bloodstream. It is formed from the carboxy terminus of a membrane-spanning protein of FNDC5⁽¹⁶⁾. Both in vivo and culture, irisin was discovered to have a strong impact on the browning of several white adipose tissues. Furthermore, a significant upregulation of UCP1 mRNA and other recognized brown fat genes occurred simultaneously with the increase in uncoupled respiration. However, WAT-specific genes were downregulated⁽¹⁶⁾.

FNDC5:

It has been discovered that the transmembrane protein FNDC5 has a signal peptide, two fibronectin domains, and one hydrophobic domain inserted into the cell membrane⁽¹⁷⁾. FNDC5 was discovered to express strongly in skeletal muscle, the pericardium, and the rectum, and moderately in the heart, the cerebral artery, the tongue, and the optic nerve. Brain tissue revealed very little expression, which conflicts with earlier mouse research⁽¹⁸⁾. It was found that in obese males with low growth hormone, skeletal muscle FNDC5 mRNA was positively correlated with insulin-like growth factor-1 gene expression, mitochondrial activity, and mitochondrial-related gene expression. This showed that FNDC5 may have a local regulatory function in skeletal

muscle even in the presence of low growth hormone⁽¹⁹⁾.

A brown fat gene program, which has been found in mice, was produced by muscle-specific overexpression of PGC-1 α , which is a member of the peroxisome proliferator-activated receptor family⁽¹⁶⁾. Not only are mice that overexpress PGC-1 α resistant to obesity, but they are also more likely to develop multilocular and UCP1-positive adipocytes⁽²⁰⁾. FNDC5, which is split by a protease to release irisin into circulation, was discovered through analysis of the PGC-1-activated muscle genes. Irisin can increase oxygen uptake and thermogenesis in people with white fat cell nephropathy⁽²¹⁾.

The metabolic role of FNDC5 polymorphisms:

In various human nations, FNDC5 gene variants may be associated with both wellness and sickness, according to a growing body of research. For instance, a study done by Staiger et al revealed that two SNPs of FNDC5 were strongly linked with insulin sensitivity⁽²²⁾. In contrast to controls who were not obese, the same two SNPs studied by Staiger et al were also discovered to be pertinent to obesity in an Egyptian population⁽²³⁾. Further research revealed that the SNP rs16835198 dominant allele G was strongly correlated with values of fasting insulin and tightly influenced by BMI⁽²⁴⁾.

Five SNPs of FNDC5 were genotyped by Al-Daghri et al to investigate the relationships between metabolic state and the FNDC5 gene variations, and they discovered that the G allele of the rs1746661 gene has been linked to increased triglyceride levels, the rs3480 GG variant to be associated with lower BMI values and a decreased weight gain, and as well as the rs1570569 TT variant

being related to higher fasting insulin levels⁽²⁵⁾.

The FNDC5 variant rs3480 G allele was linked to higher HbA1c values, whereas the rs1746661 T allele has been linked to elevated systolic blood pressure, elevated cholesterol, increased Low - density lipoprotein cholesterol, and reduced High - density lipoprotein only in women with type II diabetes mellitus but not in men.⁽²⁶⁾

Yang, et al. conducted a meta-analysis, and they found a statistically significant correlation between the SNP FNDC5 rs3480 (G/A) and the probability of developing type 2 diabetes among homozygotes (GG) versus heterozygotes (GA), While they did not find an association between rs16835198 and susceptibility to T2DM⁽²⁷⁾

It was discovered that individuals with T2DM had serum irisin levels that were lesser than those of control individuals⁽²⁸⁾, a valid explanation could be the reduced amount of PGC-1 α in skeletal muscle in conditions like Polycystic ovary and type-2 diabetes that have considerable insulin resistance⁽²⁹⁾, and this is contradictory to García-Fontana, et al.(2016) who observed that people with diabetes mellitus type 2 have higher serum irisin levels⁽³⁰⁾.

It was revealed that irisin, which is generated with physical activity, can decrease insulin sensitivity and increase it, this finding may have significant therapeutic significance for controlling blood glucose and insulin levels.

Role of FNDC5 polymorphisms on diabetic nephropathy:

Studies of FNDC5 SNPs polymorphism on nephropathies at all, and on diabetic nephropathy per se, are limited and results are few.

Previous research has demonstrated that miRNA135-5p predominantly adheres to

rs3480's G allele attenuating the effect on FNDC5 and decreasing FNDC5 mRNA levels, which results in a diminished regulatory influence of FNDC5 on metabolic disorders⁽³¹⁾. In addition, patients with diabetic nephropathy had elevated levels of miRNA-135-5p in both serum and renal tissue. These findings imply that the G allele of rs3480 has a negative impact on the production of FNDC5, which may help to explain the connection between T2DM and the G allele⁽³²⁾.

One Egyptian study done by Khidr, et al. (2017), demonstrated that the FNDC5 gene's rs16835198 G > T polymorphism significantly protects Egyptians from T2DM without affecting nephropathy or serum irisin levels.⁽²⁸⁾

It was found that irisin was inversely connected with blood urea nitrogen and serum creatinine levels in individuals with chronic renal disease by (58%) in comparison with healthy persons⁽³³⁾, even though it is also said that irisin expression is unrelated to the presence of diabetes in humans⁽³⁴⁾. Reduced levels of irisin (8%) in the blood are found in patients with T2DM and renal failure, and they have a significant relationship with the glomerular filtration rate estimation⁽³⁵⁾. In comparison to T2DM patients with normoalbuminuria and microalbuminuria, it was found that individuals with macroalbuminuria had considerably reduced serum irisin levels⁽³⁶⁾. It seems that the protein-bound uremic toxin indoxyl sulfate lowers FNDC5 transcriptional activity in cells of skeletal muscle and the level of irisin in the cell culture media, although the exact cause underlying the decrease in irisin in CKD is yet unknown⁽³⁷⁾. The findings, in the opinion of the authors, provide solid proof of how uremia might impact irisin levels. According to

studies, irisin may be used to treat individuals with chronic kidney disease (CKD) who suffer from metabolic diseases despite the limitations of this investigation⁽³⁸⁾.

Conclusion:

In conclusion, the relationship between FNDC5 gene polymorphism and irisin level in type 2 diabetes mellitus with nephropathy is still not apparent and studies are still necessary to deepen, in a different population, to give more accurate and sufficient results.

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