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A review on relationship between Diabetes and IRS-1, PC-1 Gene

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Abstract:

Diabetes is characterizes by hyperglycemia and glucose intolerance, due to the insufficiency of insulin and/or impaired effectiveness of insulin action. DM is classified on the basis of an etiology and clinical presentation of the disorder into three types: type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), and gestational diabetes . T1DM usually accounts for only a minority of the total burden of diabetes in a population; it is the predominant form of the disease in younger age groups in most high-income countries. T2DM constitutes about 85 to 95% of all diabetes cases in high-income countries and accounts for an even higher percentage in low- and middle-income countries. The incidence and prevalence of T2DM are also reported to be increasing in children.

Keywords : Diabetes, TIDM, T2DM, PC-1, IRS-1

Introduction:

Diabetes mellitus is a group of metabolic diseases characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action, or both.Diabetes mellitus is rising to an alarming epidemic level.It is observed that every population in this world suffering from Diabetes mellitus (DM) and other forms of glucose intolerance, mainly Impaired Glucose Tolerance (IGT). DM is classified on the basis of an etiology and clinical presentation of the disorder into three types: type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), and gestational diabetes [Umegaki*et al.* 2012]. The incidence and prevalence of T2DMare also reported to be increasing in children. Studies from America and Japan have demonstrated an increasing occurrence (Kitagawa *et al.*1998)

while other ethnic groups with high adult diabetes prevalence such as the Pima Indians,are also reporting increasing adolescent prevalence.(Fagot-Campagna*et al.*2000).

Work done in India & World:

Insulin receptor substrate-1 (IRS1) is a substrate of the insulin receptor tyrosine kinase and appears to have a central role in the insulin-stimulated signal transduction pathway. Therefore, the IRS1 gene has been studied extensively as a candidate gene for T2DM.

Laakso *et al.* (1994) identified three variations that predict amino acid substitutions: Gly81Arg, Ser892Gly, and Gly971Arg.

Almind *et al.* (1996) proposed that the Gly971Arg substitution could impair insulin-stimulated signaling and contribute to insulin resistance in normal and diabetic populations. The same group also showed that subjects with the 971Arg allele had significantly lower fasting plasma insulin with C-peptide levels.

Kovacs *et al.* (2003) concluded from his study that the insulin receptor substrate-1 (IRS1) is a critical element in insulin-signaling pathways, and mutations in the IRS1 gene have been reported to have a role in determining susceptibility to traits related to T2DM.

Abate *et al.* (2003) observed that the genetic susceptibility may be responsible for high prevalence of insulin resistance in Asian Indians. They studied samples of local Asian Indians and Caucasians to determine whether insulin receptor substrate-1 (IRS-1) G972A polymorphisms contribute significantly in susceptibility to insulin resistance. The frequency of carrying at least one copy of the IRS-1 972A variant in Asian Indians was similar with that in Caucasians (6% and 7%). According to them, IRS-1 972A was not associated with any change in insulin sensitivity.

McGettrick *et al.* (2004) concluded that introduction of the G972R polymorphism into the peptide reduced the amount of tyrosine phosphorylation by >60%. Pull-down experiments indicated that there was an association between the IRS-1-(925–1008) peptide and the

insulin receptor that was markedly enhanced by the presence of the G972R polymorphism. The use of additional overlapping fragments localized this interaction to domains between residues 950–986 of IRS-1 and residues 966–1271 of the insulin receptor, containing the tyrosine kinase domain of the receptor. In addition, the IRS-1-(925–1008) G972R peptide acted as a competitive inhibitor of insulin receptor and insulin-like growth factor- 1 receptor autophosphorylation. Taken together, these data indicate that the G972R naturally occurring polymorphism of IRS-1 not only reduces phosphorylation of the substrate but allows IRS-1 to act as an inhibitor of the insulin receptor kinase, producing global insulin resistance.

Antonio *et al.* (1999) describe that there is a novel polymorphism in exon 4 of the PC-1 gene (K121Q) and demonstrate that it is strongly associated with insulin resistance in 121 healthy nonobese (BMI<30 kg/m2), nondiabetic (by oral glucose tolerance test [OGTT]) Caucasians from Sicily. Compared with 80 KK subjects, Q allele carriers (n = 41, 39 KQ and 2 QQ) showed higher glucose and insulin levels during OGTT ($P < 0.001$ by two-way analysis of variance) and insulin resistance by euglycemic clamp (M value = 5.25 ± 1.38 [n = 24] vs. 6.30 ± 1.39 $mg \cdot kg^{-1} \cdot min^{-1}$ [n = 49], $P = 0.005$). Q carriers had higher risk of being hyperinsulinemic and insulin resistant (odds ratio [CI]: 2.99 [1.28–7.0], $P < 0.001$). Insulin receptor autophosphorylation was reduced ($P < 0.01$) in cultured skin fibroblasts from KQ versus KK subjects. Skeletal muscle PC-1 content was not different in 11 KQ versus 32 KK subjects (33 ± 16.1 vs. 17.5 ± 15 ng/mg protein, $P = 0.3$). These results suggest a cause-effect relationship between the Q carrying genotype and the insulin resistance phenotype and raise the possibility that PC-1 genotyping could identify individuals who are at risk of developing insulin resistance, a condition that predisposes to T2DM and coronary artery disease (CAD).

Gu *et al.* (2000) studied whether there is an association between the single nucleotide polymorphism c.533A>C (K121Q) in the glycoprotein PC-1 gene and features of the metabolic syndrome in case-control and intrafamily association studies in 922 subjects from Finland and Sweden. No difference was observed in the Q allele frequency between control subjects and type 2 diabetic subjects (12.9 vs. 15.1%). The QK genotype was associated with higher fasting plasma glucose (FPG) concentrations than the KK genotype in type 2 diabetic patients ($P < 0.001$) and their relatives ($P < 0.05$). A permutation test of siblings discordant for the QK and KK genotypes also showed that the nondiabetic siblings with the QK genotype had higher FPG (6.1 ± 2.0 vs. 5.4 ± 0.6 mmol/l, $P < 0.001$) and fasting insulin (7.0 ± 3.6 vs. 4.8 ± 2.6 mU/l, $P < 0.05$) concentrations than the carriers of the KK genotype. In addition, diabetic siblings with the QK genotype had higher systolic blood pressure (147.0 ± 18.0 vs. 140.0 ± 18.7 mmHg, $P < 0.05$) and higher fasting (9.9 ± 3.0 vs. 8.8 ± 2.8 mmol/l, $P < 0.05$) and 2-h plasma glucose (17.3 ± 8.5 vs. 12.9 ± 4.2 mmol/l, $P < 0.05$) concentrations than the diabetic carriers of the KK genotype. The present study shows that, although the Q allele of the human glycoprotein PC-1 gene is associated with surrogate measures of insulin resistance, it may not be enough to increase the susceptibility to T2DM.

Abate *et al.* (2003) observed that genetic susceptibility may be responsible for high prevalence of insulin resistance in Asian Indians. The frequency of carrying at least one copy of the PC-1 121Q variant in Asian Indians was significantly higher than that in Caucasians (P0.01), but the frequency was similar for IRS-1 972A (6% and 7%). A significantly higher insulin area under the curve during oral glucose tolerance testing ($P < 0.0001$) and lower insulin sensitivity during hyperinsulinemic-euglycemic clamps (P 0.04) was found in Asian Indians with PC-1 121Q variant compared with Asian Indians with wild-type PC-1 and with Caucasians with or without the polymorphism. They conclude

that the PC-1 K121Q polymorphism is associated with primary insulin resistance in migrant Asian Indians. Thus, a relatively high frequency of this polymorphism may be one factor contributing to insulin resistance susceptibility in Asian Indians.

According to **González-Sánchez *et al.* (2003)** overall Q allele frequency was 0.14, with no differences between obese and nonobese individuals (0.15 vs. 0.13). After adjustment for sex, age, BMI, and degree of glucose tolerance, the Q allele was associated with high plasma leptin and triglyceride levels, but not with insulin resistance.

Kubaszek *et al.* (2004) found that the effect of the PC-1 gene polymorphism on insulin levels and insulin sensitivity, measured as the homeostasis model assessment for insulin resistance, depended on birth length because fasting insulin levels and insulin resistance were highest in subjects carrying the 121Q allele who were small at birth (P for interaction 0.04 and 0.05). Additionally, in those whose birth length was up to 49 cm, the K121Q polymorphism of the PC-1 gene was associated with a 2-fold higher incidence of T2DM. Moreover, subjects who were short at birth and who had the 121Q allele had the highest incidence (31.6%) of T2DM together with hypertension. They conclude that the interaction between the K121Q polymorphism of the PC-1 gene and birth length affects insulin sensitivity and increases susceptibility to T2DM and hypertension in adulthood.

Chen *et al.* (2006) concluded that ENPP1 polymorphism was not associated with T2DM. Ectoenzyme nucleotide pyrophosphate phosphodiesterase 1 (ENPP1) is known to influence insulin sensitivity by inhibiting insulin receptor signaling. A DNA polymorphism in the ENPP1 gene at exon 4 (K121Q) was demonstrated to be associated with insulin resistance, T2DM, and a risk of early myocardial infarction, albeit with controversy. The genotype distributions or Q-allele frequency were not statistically different between the diabetic and non-diabetic groups. The anthropometric parameters, systolic and diastolic blood pressures, lipid profiles, and serum creatinine levels of subjects with different ENPP1

K121Q polymorphisms were not statistically different in the two groups or even in the pooled data. When sub-group analyzes of diabetic subjects were stratified according to BMI levels (greater or less than 27), gender, the age of diabetes onset (older or younger than 60 years), and the presence or absence of a diabetic family history; this polymorphism was still not associated with T2DM. Nor was the ENPP1 K121Q polymorphism associated with the prevalence of CAD and ischemic cerebrovascular disease in patients with T2DM.

According to **Keshavarz *et al.* (2006)** no significant difference was observed in either genotype distribution (P=0.95) or allele frequency (P=0.83) between T2DM and control groups. Notably, the frequency of the ancestral Q121 allele, which is also present in other primates, was quite high in African- Americans, and showed a marked ethnic variation (77.3% in African-Americans, 16.7% in European Americans, 10.5% in Japanese and 4.2% in Han Chinese).Consequently, the pair wise FST value (a classic measure of genetic distance between pairs of population) showed highly significant differences between African- American and non-African-American populations (FST>0.3). Our results indicated that the K121Q variant of the ENPP1 gene has very little, if any, impact on T2D susceptibility in Japanese, but may play a role in the inter-ethnic variability in insulin resistance and T2DM.

Leitão *et al.* (2008) carried out study to analyze the frequency of K121Q polymorphism in the ENPP1 gene of Brazilian subjects according to ethnic origin and to determine its possible association with T2DM and diabetic complications. They reported that ENPP1 polymorphism K121Q is more prevalent among Brazilian individual of African descendant independent of glycemic status or insulin sensitivity indexes. The Q allele frequency was increased in African descendant T2DM patients (KK= 25.9%, KQ= 48.2% and QQ= 25.9%) and control subjects (KK= 22.0%, KQ= 53.8% and QQ= 24.2%) compared to

European descendant T2DM patients (KK= 62.7%, KQ= 33.3% and QQ= 4.1%) and control subjects (KK= 61.0%, KQ= 35.6% and QQ= 3.4%).

In one of the recent studies conducted in Serbia by **Lazarevic *et al.*(2008)** the prevalence of the PC-1 121Q allele was significantly higher in T2DM+Coronary Heart Disease(CHD), compared to T2DM ($P < 0.001$) and control ($P < 0.001$) groups, since it was found in 10 (14%) T2DM patients, 13 (41%) T2DM+CHD patients and 10 (17%) control subjects. When the association of PC-1 121Q allele and the risk of suffering from CHD were assessed within the T2DM group PC-1 121Q allele carriers had a 76% lower risk (OR 0.24; 95% CI: 0.08-0.67, $P = 0.006$) for developing CHD compared to subjects who exhibited PC-1 wild-type. The prevalence of the PC-1 121Q allele was significantly higher in T2DM patients who suffered from CHD, compared to T2DM patients without CHD. However, PC-1 121Q allele carriers had a 76% lower risk (OR 0.24; 95% CI: 0.08-0.67, $P = 0.006$) for developing CHD compared to subjects who exhibited PC-1 wild-type. Since these data were cross-sectional, the potential patient selection and survival bias, as well as community under diagnosis of T2DM and CHD, could most likely substantially underestimate the genetic influence.

Seo *et al.* (2008) carried out a study to predict the association of K121Q polymorphism with T2DM or obesity in Korean male workers. The results of his study demonstrated that the ENPP1 121Q genotype (KQ+QQ types) was not associated with T2DM (odds ratios [OR], 0.854; 95% confidence interval [CI], 0.571-1.278) or obesity (OR, 0.933; 95% CI, 0.731-1.190). In addition, the frequency of the Q allele was not related to T2DM (OR, 0.911; 95% CI, 0.630-1.319) or obesity (OR, 0.962; 95% CI, 0.767-1.205). They concluded that the ENPP1 121Q allele is not a critical determinant for either diabetes or obesity in Korean males.

González-Sánchez *et al.* (2008) in their study from the province of Segovia in Central Spain (Castille), concluded that the ENPP1121Q allele might contribute to the genetic susceptibility for abdominal obesity among subjects with metabolic syndrome.

Bouhaha*et al.* (2008) conducted a study at Tunisia to study the effect of PC-1-K121Q polymorphism on the genetic susceptibility to T2DM in the Tunisian population. They found that genetic variation at PC-1-K121Q predisposes to T2DM in the Tunisian population (OR=1.55, 95%CI [1.11-2.16], p=0.007). Their findings support the hypothesis that ENPP1-121Q is involved in the genetic susceptibility of T2DM in the Tunisian population.

Sharma JK *et al.* (2014) reported in the population from Jaipur, Rajasthan, India that the K121Q polymorphism is moderate ranging from 25-30% that shows significant positive correlation with fasting blood sugar (FBS) in different genotypes.

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