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Genetic Links between Coronary Artery Disease and Type 2 Diabetes

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ABSTRACT:
Type 2 diabetes (T2D) is characterized by chronic hyperglycaemia with disturbances of carbohydrate, fat and lipid metabolism resulting from defects in insulin secretion, action or both. Cardiovascular morbidity and mortality is high among T2D subjects and of all the complications of T2D individuals, Coronary artery disease (CAD) is the most common and life threatening. It has been found that risk for CAD is high among diabetic subjects by the factor of 2 to 4 as compared to non diabetic subjects. T2D has been associated with endothelial dysfunction as it increases the inflammation and insulin resistance resulting in the increase of oxidized low density lipoprotein, endothelin 1, angiotensin II, oxidative stress and decreasing the action of nitric oxide and insulin or growth factors in endothelial cells. The candidate genes for T2D are potential candidate genes for CAD also because of the overlap of the various metabolic and hormonal derangements in both the conditions. Among these, genes like TCF7L2, ACE, PPAR gamma, IRS1, Adiponectin and TNF alpha have emerged as main candidate genes linking both the conditions. In the GWAS studies a common locus on 9p21.3 (ANRIL) has been found for both the diseases. In spite of a shared pathophysiology between both the conditions reports for their genetic association are scarce. Thus there is a strong need for further studies and development of a strategy for the prevention of CAD long before its onset in T2D patients. In this review we focused on the various pathophysiological links (insulin resistance, hyperglycaemia, inflammation, and defect in fibrinolytic and coagulation factors, dyslipidaemia) and genetic links between T2D and CAD.
Key words: T2D, CAD, hyperglycaemia, insulin resistance, dyslipidemia

INTRODUCTION:

Diabetes is a group of metabolic diseases characterized by hyperglycaemia resulting from defects in insulin secretion, insulin action or both. Chronic hyperglycaemia results in long term damage, dysfunction and failure of different organs especially heart, eyes, kidneys and blood vessels (ADA, 2012). Diabetes is becoming an epidemic and its worldwide prevalence is expected to increase up to 7.7% among adults by 2030. In just 20y, between 2010 and 2030 there will be 69% and 20% increase in number of adults with diabetes in developing and developed countries respectively (Shaw *et al*, 2009).

Type 2 Diabetes (T2D) constitutes about 90% of diabetes cases. Cardiovascular morbidity and mortality is a major burden in T2D patients and among all of them, CAD (Coronary Artery Disease) is the most common and dangerous one. Indians are racially more predisposed to T2D and premature CAD as explained by their Asian Indian phenotype, insulin resistance and greater abdominal obesity (Higher waist circumference despite lower body mass index) (Mohan *et al*, 2010).

Diabetes as a risk factor for CAD

CAD is a pathophysiological condition in which occlusion of coronary arteries occurs, which often results in myocardial infarction (MI). Risk for CAD is high among diabetic subjects by the factor of 2 to 4 as compared to non diabetic subjects, as various risk factors are common in both the conditions like age, obesity, physical inactivity, dyslipidemia, insulin resistance, smoking etc. (Deepa *et al.* 2002).Thus, high prevalence of diabetes directly or indirectly increases the burden of CAD. Atherosclerosis is the major cause of CAD which results due to various factors contributing to endothelial dysfunction including decreased production of NO; a potent vasodilator and a major factor responsible for normal endothelial function.T2D is associated with endothelial dysfunction by increasing oxidized low density lipoprotein, endothelin 1, angiotensin II, oxidative stress and decreasing the action of insulin or growth factors in endothelial cells. The mechanisms may include impaired release or destruction of NO (Kobayashi *et al*, 2005). Atherosclerotic plaques which are responsible for the progression of CAD are more extensive, diffused, have many different branches and are more prone to instability and rupture in T2D patients as compared to plaques of non diabetic individuals (Marchetti *et al,* 2007). There is an overall increased atherosclerotic plaque burden and 3.5 fold high risk of coronary stenosis independent of other cardiovascular risk factors in diabetic individuals(Yoo *et al*,2009).Further, diabetes has an important role in pathogenesis of CAD by increasing the risk of hypertension,hypertriglyceridemia, low high density lipoprotein (HDL) cholesterol,PAI-1 (plasminogen activator inhibitor-1) and Fibrinogen Levels. The Framingham heart study(Abott *et al,* 1988) was the first one to demonstrate that there is a 3.5 to 4 fold increased risk of CAD mortality among diabetic men and women as compared to the nondiabetic individuals. In a population based study, the Chennai Urban population study (CUPS) involving two residential areas of Chennai (South India), it was found that total prevalence of CAD was 9.1% in NGT(normal glucose tolerance) subjects, 14.9% in IGT(impaired glucose tolerance) subjects and

21.4% in diabetic subjects (Mohan *et al.* 2001). A strong association between CAD and diabetes has been found inspite of wide ethnic and geographic variations in their prevalence (Mohan *et al*,2010).

For this review, a general internet and Pub Med search was carried out to find the relevant literature from 1980-2012 on the pathophysiological and genetic link between CAD and T2D.The review is focussing on the various pathophysiological links (hyperglycaemia, inflammation, insulin resistance, inflammation, dyslipidemia, defect in fibrinolytic and coagulation factors) and genetic links as evident from candidate gene studies and GWAS between CAD and T2D to get a clear picture for their association.

PATHOPHYSIOLOGY

Role of insulin resistance

Insulin resistance is defined as the decrease in the ability of insulin to promote glucose uptake in the skeletal muscle and adipose tissue and to suppress hepatic glucose output, which may be present for many years before the development of any abnormality in plasma glucose levels (Haffner, 2003). It is associated with a number of classical risk factors for CVD like central obesity, general obesity, elevated blood pressure, elevated levels of total triglycerides, activation of renin angiotensin system, increased reactive oxygen species (ROS) production, low levels of high density lipoprotein (HDL) cholesterol and glycotoxicity; each of them is an independent cardiovascular risk factor (Laakso, 2010; Rains *et al*, 2011). It has been found in various studies that insulin resistance is the independent risk factor for CVD (Bonora *et al*, 2005; Eddy *et al,* 2009). Nitric oxide (NO) is a potent vasodilator and is produced in the endothelial cells by the stimulation of nitric oxide synthase (eNos) by PI3- Akt pathway. As a result of insulin resistance, a molecular defect in the insulin signalling occurs, which results in the impaired activation of PI3- Akt pathway leading to the impaired production of NO. On the other hand MAP- kinase pathway is stimulated which results in the release of E-selectin and VCAM, Endothelin 1, various inflammatory cytokines, migration and proliferation of vascular smooth muscle cells leading to vasoconstriction and atherosclerosis (Laakso ,2010)(Fig 1).

Role of hyperglycaemia

Hyperglycemia is one of the major contributing factor to the pathogenesis of various diabetic complications including atherosclerosis. Superoxide overproduction by mitochondrial electron transport chain (ETC) induced by hyperglycaemia is the key step for the stimulation of other pathways like: Polyol pathway, Hexosamine pathway, Activation of protein kinase C and AGE pathway. The activation of PKC and hexosamine pathway lead to the increased expression of various inflammatory and pro-inflammatory cytokines (Ceriello, 2011)(Fig 2) . ROS are produced by glucose autoxidation, glucosamine formation, oxidative phosphorylation and can directly damage endothelial cells as well as by oxidising LDL and AGEs (Marchetti *et al,* 2007). ROS formed by hyperglycaemia inhibits NO production and prevents the migration of vascular smooth muscle cells into plaques, which is the necessary step for the stabilization of the plaque (Moreno *et al*, 2004; D' Souza *et al*, 2009). The unstabilized plaques are more vulnerable to rupture leading to thrombosis and hence atherosclerosis. Advanced glycation end products formed as a result of the non enzymatic reaction between glucose and arterial wall protein accelerate atherosclerosis by directly interfering in the arterial wall (Chiha *et al*, 2012).

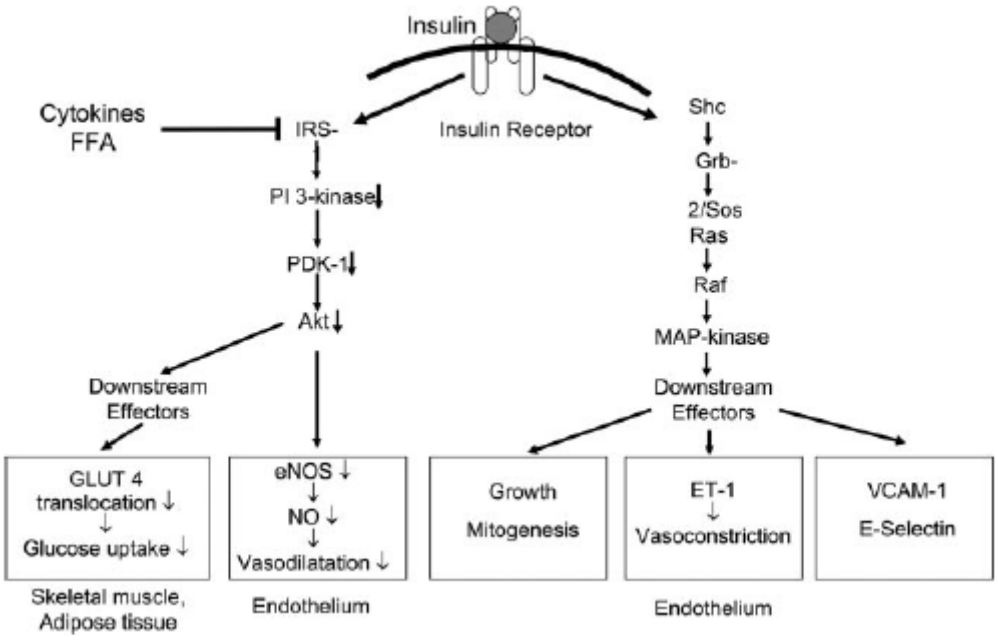

Fig 1: Parallel insulin signalling pathways (Adapted from Laakso *et al*, 2010)

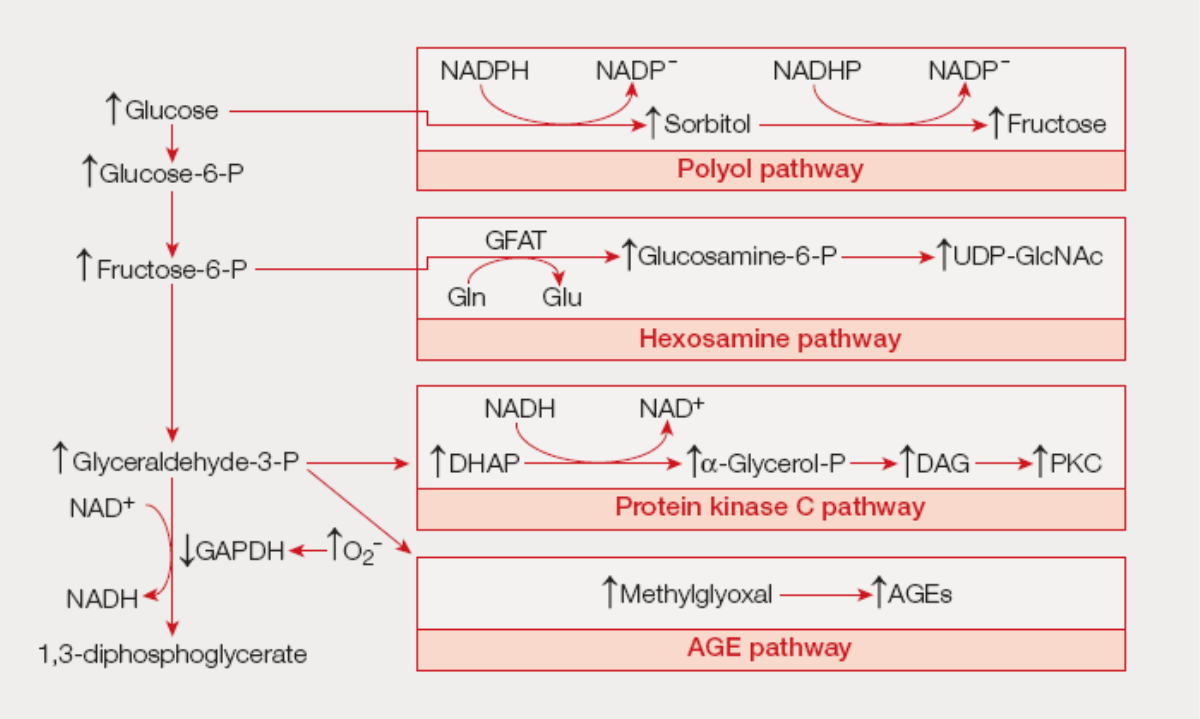

Fig 2: Mechanisms leading to hyperglycemia induced damage (Adapted from Ceriello, 2011).

Role of inflammation

It has been found that various pathways of insulin signalling and inflammation are tightly linked leading to insulin resistance and atherosclerosis (Laakso, 2010). Low grade inflammation is the hallmark of T2D and atherosclerosis. In T2D, activation of inflammation results from obesity and insulin resistance. As a result of T2D, a acute phase reaction occurs in which a large number of inflammatory and pro-inflammatory cytokines are released from adipose tissue (Pickup *et al,* 2004). Adipocytes release cytokines (TNF alpha, IL-6, PA-1), adipokines (adiponectin and leptin) which are associated with CVD. Among them adiponectin has a anti inflammatory role and hence protects against atherosclerosis (Callaberro *et al*, 2003; Kadowaki *et al*, 2005; Murodola *et al*, 2006). Angiotensin II is found to induce oxidative stress resulting in the up regulation of the pro-inflammatory transcription factors like kappa B, which results in the upregulation of various inflammatory markers leading to endothelial dysfunction (Savoia *et al,* 2007). In vascular endothelium of T2D patients, Monocyte chemoattractant protein 1 and macrophage migration inhibitor factor are released and expression of various adhesion molecules like VCAM, ICAM, E- selectin occurs, as a result monocytes are attracted towards them .Thus the continuing cascade of inflammation occurs by releasing

various pro-inflammatory cytokines like TNF alpha, IL-1, IL-6, IL -18 (Libby *et al*, 2002; Christianen *et al*,2005; Ehes *et al*, 2008) leading to atherosclerosis.

Role of defect in fibrinolytic, coagulation factors and dyslipidaemia

A number of lipid abnormalities are associated with T2D which includes increased concentration of total cholesterol, low density lipoprotein (LDL) cholesterol, triglycerides and low concentration of HDL. The anti atherogenic role of HDL particles is by increasing reverse cholesterol transport, protecting endothelial cells by activating eNOS and NO release, attenuating the expression of VCAM-1, ICAM-1, E-Selectin and IL-8 and by reducing apoptosis and oxidative stress by inhibiting LDL oxidation and preventing lipid hydroperoxide formation (Marchetti *et al*,2007). In Asian Indians, triglyceride/HDL ratio of 3 has been proposed to be used as a surrogate marker for small LDL particles as these are associated with both CAD and diabetes (Mohan *et al*, 2005). Hypertriglyceridemia has been found to be an independent risk factor for cardiovascular disease (CVD) in patients with diabetes mellitus (Cullen *et al*, 2000). Low density lipoprotein (LDL) levels are similar in the patients as compared to the non diabetic individuals but are dominated by small, denser and more atherogenic LDL particles (Eckel *et al*, 2002).Different scavenger receptors on macrophages and smooth muscle cells (SMC) uptakes modified lipoproteins (glycated, oxidated and glycooxidated) and as a result, intracellular accumulation of lipids and lesion formation occurs. Modified proteins and lipids lead to the increased production of procoagulants, adhesion molecules and cytokines resulting in atherosclerosis (Mazzone *et al,* 2000).

Thrombus formation and dissolution of plaque is the most dangerous step in CAD, resulting from the defect in various fibrinolytic and coagulation factors. The fibrinolytic and coagulation cascade consisting of activators and inhibitors play a major role in pathological mechanisms leading to CAD (Deepa *et al*, 2002). In T2D patients, enhanced thrombus formation occurs due to increased platelet activity and coagulability of blood. It is seen that advanced atherosclerotic lesions in diabetes patients are more vulnerable for rupture as they have reduced number of vascular muscle cells (Laakso,2010) .In T2D patients pathological alterations of fibrinogen, blood rheology, and plasminogen activator inhibitor are of major relevance for short term incidence of cardiac events (Jax *et al*,2009)

GENETIC LINK BETWEEN CAD AND DIABETES

T2D and CAD share a striking similarity in their pathogenesis, due to the coexistence of common effectors, mainly insulin resistance and hyperglycaemia. Thus hypothetically all the candidate genes for diabetes are the potential candidate genes for CAD (Fig 3). There are a number of studies on the association of various genes with T2D but it is not clear that how many of them are responsible for increased CAD risk.

Apart from the genes related to insulin resistance and hyperglycaemia, genes from other pathway are also important as various metabolic derangements are common between both the conditions. Inspite of the striking similarity between both the diseases, there is very little information about their genetic association.

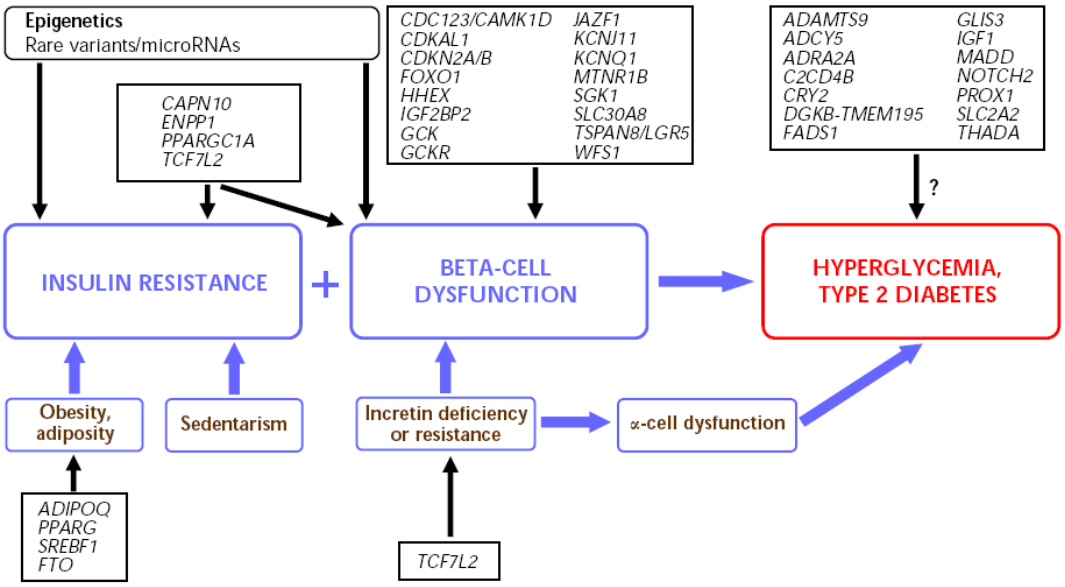

Fig 3: Possible mechanisms of confirmed and potential candidate genes in T2D (Adapted from Sousa *et al*, 2011)

Various approaches have been used for the search of diseased genes, out of them candidate gene approach and Genome wide association studies (GWAS) are of paramount importance. Candidate genes studies remain the major approach as they involve the study of the genes in the already implicated metabolic pathway of T2D like genes in the pathway mediating production of cellular toxins in response to excess glucose and genes involved in the tissue specific organ damage induced by these toxins, despite of a number of false positives due to marginal 'P' or false negatives due to lack of the statistical power (Sousa *et al*, 2011). Based on candidate gene analysis, we have

provided brief descriptions of major genes which have been studied comprehensively in both the diseases across the globe to establish the genetic link between CAD and T2D

MAJOR CANDIDATE GENES FOR T2D IMPLICATED IN CAD

1. **PPAR gamma**:

Chromosomal location and Function: Peroxisome proliferator activated receptor gamma (PPARγ or PPARG) present on 3p25 is a transcription factor. It is highly expressed in adipose tissue and macrophages, where it is involved in adipocyte differentiation, triglyceride synthesis, glucose homeostasis and fatty acid trapping (Semple *et al.*2006). It also regulates the release of various adipokines including tumour necrosis factor alpha, angiotensinogen (AGT), interleukin- 6(IL6) and plasminogen activator inhibitor 1(PA-1)(Ahima *et al,* 2000). It has also has an effect on vasculature by its expression in endothelial cells (decrease in endothelin 1, lox-1, NO release), vascular smooth muscle cells (decrease in MP-9), Macrophages (increase in cholesterol efflux, decrease in cytokines and MMP-9), and T cells (decrease of cytokines) (Plutzky 2004).

Studies for association with T2D

PPARG is the most extensively studied PPAR. Among all the polymorphisms in PPAR gamma, Pro12 Ala and C1431T polymorphisms have been studied in various populations with conflicting reports for their association with T2D.

Pro12Ala: Ala 12 allele for Pro12Ala polymorphism was found out to confer protection in Japanese (Mori *et al*, 2001), Iranian (Meshkani *et al*, 2007), Danish (Frederiksen *et al,* 2002) and American Caucasian (Memsoglu *et al,* 2003) populations. In a metaanalysis of 41 published and 2 unpublished studies (Ludovico *et al*, 2007) Ala12 variant was found out to be associated with 19% T2D risk reduction but its effect was highly heterogeneous. The risk reduction in Europe was very heterogeneous being progressively smaller from northern (26%) to central (10%) and Southern (0%) Europe. Risk reduction was highest in Asia. Again the association of Pro12 Ala was confirmed in Asian Indian Sikhs and it emerged as a strongest predictor of T2D (Sanghera *et al*, 2010).

C1431T: Another polymorphism C1431T in *PPAR gamma* has been studied less extensively in relation with T2D and metabolic syndrome. It is often found out to be in

linkage disequilibrium with Pro12Ala polymorphism. T allele has been reportedly associated with reduced risk of CAD (Zhou *et al.*2011) In Chinese Han population from Beijing (China) a correlation with Pro12Ala and C1431T genotypes, insulin resistance and metabolic syndrome was found(Donxia *et al,* 2008). Both polymorphisms showed a non significant association with metabolic syndrome components but a significant association with insulin resistance. Also both Ala and T allele carriers had a higher BMI. In an another study, the association of Pro12Ala and C1431T variants of PPAR γ and their haplotypes with the susceptibility of T2D was confirmed and Pro12Ala was found out to be associated with lower body mass index in T2D patients, whereas no difference was observed in the distribution of Pro12Ala- C1431T haplotypes between patients and controls (Mohamed *et.al*.,2007). Both the polymorphisms have been studied in various populations for association with CAD with inconclusive results (Table 1).

Table 1: Studies of polymorphisms in *PPAR Gamma* with CAD

Gene	**Variant**	**Disease**	**Sample size (population)**	**Result**	**Reference**
PPAR gamma	C1431T	CAD	864 patients/1008 controls (Chinese Han)	T allele associated with reduced risk of CAD.	Zhou *et al*, 2011
PPAR gamma	C1431T Pro12 Ala	CAD	202 patients (102 with diabetes,100 without diabetes) (Turkish)	C1431 CT has unfavourable effect on serum lipid profile in CAD patients with diabetes and effect is weakened byP12P homozygotes	Yilmaz – Ayodgan *et al.*2011
PPAR gamma	Pro12Ala	CAD	478 CAD patients /218 controls	Ala 12 allele is associated with reduced risk of CAD	Gaglani *et al*,2010
PPAR gamma	Pro12Ala C1431T	CAD	5795 cases, 9069 controls	No association of Pro12Ala with CAD, whereas C1431T marginally associated with CAD	Ding *et al*, 2012 (meta analysis)

2 .***TCF7L2*:**

Chromosomal location and function: Transcription factor 7 like 2 (*TCF7L2*) gene is present on chromosome 10q25.3 and has 17 exons; 5 of them shows alternative splicing in various human tissues (Osmark *et al*, 2009). It is expressed in various tissues including placenta, lung, brain, kidney, pancreas, heart and adipocytes and has a very important role in *Wnt* signalling pathway (Cauchi *et al,* 2006).

Table 2: Studies of polymorphisms in *TCF7 L2* with CAD

Gene	Variant	Disease	Sample size (population)	Result	Reference
TCF7 L2	rs7903146 rs 12255372 rs 11196205	CAD	1,650	All the three variants are significantly associated with CAD	Muendlein *et al,* 2011
TCF7L2	Rs7903146	CAD	15792 (White and black U.S communities located in north Carolina, Missisipi, Minnesota, Maryland)	In white population significant increase in CHD risk and overall lean individuals homozygous for T allele, whereas no association in black community.	Ku-Charska – Newton *et al*,2010 (Prospective study)
TCF7L2	Rs7903146	CAD	889 subjects referred for CAD , 359 subjects Mass II trial prospectively (Brazilian)	Association with CAD severity and mortality	Sousa *et al*,2009

Studies for association with T2D: Various GWAS studies across the globe have reported *TCF7L2* as the major susceptibility gene for T2D. A number of variants in this gene were found to have a significant association with T2D. The positive association was reported in Chinese Han population by genotyping 20 variants in *TCF7l2* gene. The association of SNP rs 290487 with T2D and for CC genotype was observed with a population attributable risk fraction of 18.7%. The haplotype associated with this variant was significantly associated with T2D (Chang *et al,* 2007) .In another study (Rees *et al*, 2008), the minor allele of four variants (rs 7901695, rs7903146, rs 11196205and rs 12255372) was significantly associated with T2D, with rs 7903146 conferred nearly 1.5

fold risk of T2D. Despite the strong association of the variants of *TCF7l2* with T2D in various ethnic groups, a weak or no association was observed for rs 7903146 and rs 12255372 in Arab population (Alsmadi *et al*, 2008) and for 14 variants in Pima Indians(Guo *et al*,2007). In Indian population a strong association was observed with T2D for three variants in this gene, rs 7903146, rs 12255372 and rs 4506545. All the variants showed an increased risk when they were in homozygote state rather than heterozygote state (Chandak *et al,* 2007). After confirming *TCF7L2* as a potential candidate gene for T2D in GWAS studies, a number of studies were done for its association with CAD. Some of the latest studies were summarized in Table 2.

3. *ACE*(Angiotensin 1 converting Enzyme):

Chromosomal location and function: ACE gene is located on the chromosome 17q23 and is composed of 26 exons and 25 introns. It is a zinc metallopeptidase, and is widely distributed on the surface of endothelial and epithelial cells. It has a very important role in the two important pathophysiological systems:

1) Production of angiotensinII
2) Degradation of bradykinin(Sayed – Taba tabei, 2006)

Thus it plays a very important role in rennin angiotensin system, making it a strong candidate gene for CAD and T2D.

Studies for association with T2D: Among all the variants in this gene I/D polymorphism has been extensively studied in context of T2D. In a meta analysis, including 24 studies in 15,166 subjects, the D allele was associated with 14% increased risk of T2D relative to I variant(Zhou *et al,* 2010). When subgroup analysis was done, a significant association in Caucasian and East Asians was observed, however lack of association was observed in Turkish Groups. Publication bias was excluded by Egger method. In another meta analysis (Niu *et al*, 2010), a total of 14 studies were included (1985 patients, 4602 controls). It was found that presence of D allele conferred a significant increased risk for T2D. Various subgroup analyses showed a significant association in African, European ancestry rather than Asian ancestry. As *ACE* has been widely studied for the susceptibility of T2D in various populations with significant results, a number of studies were done for its association with CAD. Table 3 summarizes some latest studies indicating an association of D allele with CAD.

Table 3: Studies of polymorphisms in *ACE* with CAD

Gene	Variant	Disease	Sample size (population)	Result	Reference
ACE	I/D	CAD	263 patients/264 controls (Iran)	No association	Shafiee *et al*. 2010
ACE	I/D	CAD	323 patients(Iran)	D allele independent risk actor for CAD	Vaisi-Rayagane *et a,*.2010
ACE	I/D	CAD	129 Myocardial infarction patients,101 normal subjects	Significant association D allele with CAD	Masud *et al,* 2011
ACE	I/D	CAD	647(Polish Caucasians)	DD genotype associated with severe CAD	Borzyszkowa *et al*, 2012

5. ***TNF alpha*:**

Chromosomal location and function: It is a pro-inflammatory cytokine, present on chromosomal location 6p21.3 within the MHC region (Hazeer *et al,* 2000). It has a very important role in the lipid metabolism. Apart of its inflammatory action it is widely implicated in the insulin resistance as it is involved in the down regulation of the genes involved in the insulin signalling, induction of elevation of free fatty acids (through lipolysis) and negative regulation of PPAR gamma (Moller, 2000).

Studies for the association with T2D: Among the reported genetic variations in the *TNF alpha* promoter region such as -238, -308, -857 and -1031, the -308 and -238 polymorphisms have been extensively studied. The first meta analysis for the association between TNF 338 G/A polymorphism and T2D done on overall as well as specific populations (Feg *et al,* 2009), failed to show any significant association with 338G/A polymorphism. In another Meta analysis on -308 G/A polymorphism, 18 studies were included. However this Meta analysis also failed to show any significant association with T2D (Feng *et al.* 2011). Due to the confirmed role of *TNF alpha* in inflammation and insulin resistance, it has been studied for susceptibility of CAD with varying results (Table 4)

Table 4: Studies of polymorphisms in *TNF alpha* with CAD

Gene	Variant	Disease	Sample size	Result	Reference
TNF alpha	-308 G<A	CAD	97 patients, 95 controls	G allele is associated with increased risk of CAD	Elahi *et al,* 2008
TNF alpha	-308 G<A	CAD	105 patients/190controls	No association	Giacconi *et al*, 2006
TNF alpha	-308 G<A	CAD	180 patients/ 329controls	No association	Allea *et al*, 2008
TNF alpha	-308 G<A	CAD	9921 patients/7944 controls	A allele associated with increased risk of CAD in Caucasians but not in Asians, Indians and Africans	Zhang *et al*, 2011 (Metanalysis on studies published between 1947-oct 2010)

5. ***Adiponectin***

Chromosomal location and function: It is one of the most abundant protein which is derived from adipose tissue and is encoded by adiponectin gene (ADIPQQ) located on chromosome 3q27. It has a protective role in T2D and CVD as it has anti atherogenic , anti-inflammatory and insulin sensitizing properties. The serum concentrations of adiponectin are heritable. (Commuzzie *et al*, 2001; Herd *et al*, 2006; Kawano *et al,* 2006), thus making it a strong candidate gene for T2D and CAD.

Association with T2D: There are a number of studies on adiponectin gene as it is the most promising candidate gene for T2D. A study on the role of 45 T/G polymorphism (Khodeer *et al,* 2011), revealed that individuals with TG/GG genotype were at nearly fourfold increased risk of T2D.This was in accordance with the reported results in Iranian population (Mohammadzaden *et al,* 2009) but was contradictory to reports on Polish-Caucasian population in which no significant association was observed in the G allele frequency among cases and controls (Szopa *et al*, 2008). Similar results were obtained in Italian cohort; 11391 G/A, -11377 C/G, 45 T/G and276 G/T polymorphisms were studied but only SNP 276 TT homozygotes were found to have a protective role in myocardial infarction and T2D (Chiodini *et al*, 2010). In a study on Korean population no significant

association for SNP 45 and SNP 276 was obtained (Lee *et al*, 2005).The studies on association of *Adiponectin* gene in CAD indicate association of SNP 45 T>G with increased risk and + 276 G>T with decreased risk(Table 5).

Table 5: Studies of polymorphisms in *Adiponectin* with CAD

Gene	Variant	Disease	Sample size (Population)	Result	Reference
Adiponectin	SNP45T>G SNP276 G>T	CAD, T2D	418 T2D patients out of them 123 with CAD (Saudi Arabian)	SNP45 T>G is an independent risk factor for CAD in T2D patients	Aldaghri *et al,* 2011
Adiponectin	SNP45T>G	CAD, T2D	216 T2D (Afro -carribean out of them 57 with CAD)	Associated with CAD in T2D individuals	Foucan *et al,* 2010
Adiponectin	SNP45T>G SNP276 G>T	CAD, T2D	114 T2D patients with CAD,127 T2D patients without CAD (Iranian)	T allele of +276 G>T SNP is significantly associated with decreased riskof CAD, Haplotypes 45 T-276T and45G-276 were associated with decreased risk of CAD	Esteghamate *et al*, 2011
Adiponectin	SNP45T>G	CAD	464 (Iranian)	G allele with risk of CAD	Sabouri *et al,* 2011
Adiponectin	SNP45T>G SNP276 G>T	CAD	316 (Tunisian)	Mutated genotypes +276 G/T (TT/GT) associated with reduced risk of significant coronary stenosis	Imen *et al,* 2011

6. IRS1

Chromosomal location and function: Insulin receptor substrate-1(IRS-1) is located on 2q36 and it is found to have an important role in insulin action in skeletal muscle, adipose tissue and pancreatic β cells (Nandi *et al*,2004). Apart from peripheral insulin sensitivity, it has also been found to be associated with regulation of insulin secretion by pancreatic β cell (Sesti *et al*, 2001). It is involved in the insulin signalling in adipose tissue and skeletal muscle cells and regulates muscle glucose transport, brown adipocyte differentiation and insulin induced β cell insulin secretion (White, 2002).

Table 6: Studies of polymorphisms in *IRS1* with CAD

Gene	Variant	Disease	Sample size (population)	Result	Reference
IRS1	G972R	CAD	215 patients/221 Controls (Austrian)	No association	Stohmer *et al,* 2005
IRS1	G972R	CAD	Cases 195/ controls105 (Taiwanese)	No association	Tsai *et al*, 2002
IRS1	G972R	CAD/T2D	153 unrelated offspring of T2D patients	Association with atherogenic profile in offspring of T2D diabetic patients	Marini *et al*, 2003
IRS1	G972R	CAD	318 cases/208 controls	Association with CAD	Baroni *et al,* 1999

Studies for the association with T2D: Glycine to Arginine, a missense variation in codon 972 is the most common polymorphism implicated in T2D. But the results are highly inconsistent. In a meta analysis of 27 studies published between the year 1993 and 2002 including 3408 cases and 5419 controls found that the individuals carrying the Arg 972 variant were at 25% increased risk of T2D as compared with non carriers (Jellema *et al*,2003).Another meta-analysis (Florez *et al*,2004)failed to find any association of G972R polymorphism in 9,000 individuals (4279 cases, 3532 controls, 1189 siblings)

for T2D. In a study on four polymorphisms of IRS1 gene (Pro 512 Ala, Asn 1137 Asp, G972R and Arg 158 Pro) in 444 cases and equal number of controls in Mexican population only G972R showed an association with T2D(Burguete- Garcia *et al.*2010) In a study from India on 2,148 subjects, part of the Chennai urban rural population epidemiology study (CURES), this variant was not found to be associated with T2DM in South Indian population (Bodhini *et al.* 2011). G972R polymorphism has been studied extensively in CAD, again with inconsistent results (Table 6).

Apart from the above mentioned major candidate genes of CAD and T2D, some other genes which are found to be widely associated with T2D have also been studied as the candidate genes for CAD, however there are scarcity of reports for their association with CAD. These are CALPAIN10, FAB4, GST,IL-6,IL-10 and Paraoxonase (**Table 7)**

OVERLAP BETWEEN THE GENETICS OF T2D AND CAD: RESULTS FROM GENOME WIDE ASSOCIATION STUDIES (GWAS)

In the recent years, the search for the determination of the various genetic variants in the common diseases has changed dramatically by the introduction of GWAS. A number of GWAS were done on different populations in either CAD or T2D but there have been no comprehensive GWAS report for CAD in T2D individuals. Most of the GWAS studies for CAD were done on general population. GWAS has given us the most replicated locus associated with both the diseases, present on chromosome 9p21.3 (ANRIL locus) though it is not found to be associated with a variety of classical risk factors for CVD. This locus is present near the *CDK N2 A* and *CDK N2B* genes which are involved in the cell cycle proliferation, apoptosis and aging. The various SNPs reported in this region have been found out to be in a strong linkage disequilibrium with each other. This LD block has no protein coding genes but it includes the 3' exons of the non coding ANRIL gene known as *CDKN2BAS*.(Mcpherson *et al*, 2007; Broadbent *et al*,2008)

Meta analysis of Genome Wide association studies (Wu *et al*, 2012), identified the shared genetic susceptibility locus for coronary artery disease, T2D, obesity as 6q23 - 25.3. The *ENPP1* (Ectonucleotide pyrophosphate phosphodiesterase) was found out to be the important candidate gene in this region. It encodes membrane bound glycoprotein inhibiting the insulin receptor tyrosine kinase activity. The variants of these genes were

Table 7: Studies of polymorphisms in various genes with CAD.

Gene	Variant	Disease	Sample size (population)	Result	Reference
CALPAIN 10	SNP44	CAD	85 Families (Mexican American)	Haplotype 1112 associated with increased intima media thickness (IMT), haplotype1221 decreased IMT,3SNP haplotype112/121 associated with largest IMT	Goodarzi *et al*, 2005
	SNP43				
	SNP56				
	SNP63				
FAB4	T-87C	CAD/T2D	7,899	Reduced risk of T2D and CAD	Tuncman *et al*,2006
GST	GSTM1	CAD	102 cases/100controls(South African of Indian ancestary)	Association of GST M10/0 and GSTP1 A105/A105 with CAD	Phulukdaru *et al,* 2012
	GSTP1				
	GST M1	CAD	231 T2D patients, 184 suffering from CAD	GSTM1 and GSTP1 associated with CAD in T2D individuals	Manfredi *et al,* 2009
	GSTP1				
IL-6	174 G/C	CAD	26 patients with stable angina,45with unstable angina,58 with non fatal MI (Greece)	Association with CAD	Athanossios *et al,*.2008
Paraoxonase	G192R	T2D/CAD	180 patients, Non diabetic without CAD (n=40), diabetic without CAD(45), Non diabetic with CAD (n=47), diabetic with CAD (n=48)	Independent risk factor for CAD	Elnoamary *et al,*2012
IL-10	-1082 G>A	CAD	2260 patients (Finnish)	Association of high to intermediate producer haplotype GCC with decreased arterial elasticity	Heinskanen *et al,*2010
	-819C>T				
	-592C>A				

also found out to be associated with metabolic syndrome and CAD in T2D patients (Lazaruvic *et al*, 2008; Tasic *et al,* 2007). The association of chromosomal location 9p21.1-q31.32 with T2D and CAD in addition to obesity was also confirmed by meta analysis. Despite of the lack of GWAS studies on the association of CAD and T2D some of the genes and SNPs were found out to be associated with both T2D and CAD in GWAS (Table 8).

Table 8: SNPs of the genes associated with both T2D and CAD in GWAS. (Adapted and modified from : Sousa *et al*, 2011)

Mapped gene	**Stongest SNP risk allele**	**Disease, trait/ Associated search**
TCF7L2	rs4506565	Fasting glucose-related traits/ T2D
	rs1224332	6 2-h glucose challenge/ T2D
	rs7901695	T2D,CAD/T2D,CAD
CDKN2BAS	rs564398	T2D/T2D
	rs4977574	CHD/CAD
	rs7866518	CHD/CAD
	rs7020996	T2D/T2D
	rs10811661	T2D/T2D
	rs2383208	T2D/T2D
	rs10965250	T2D/T2D
	rs1333051	T2D/T2D
	rs1333049	CHD/CAD
	rs10757278	Myocardial infarction/CAD
KIAA1486-IRS1	rs7578326	T2D/T2D
	rs2943634	CHD/CAD

CONCLUSION: In multifactorial diseases like CAD and T2D various environmental risk factors are common, as a result of which both the conditions often coexist in the same individual. T2D involves a number of metabolic derangements like hyperglycemia, insulin resistance, inflammation, dyslipidemia and each of them is an independent risk factor for CAD. The pathophysiological link between CAD and T2D is explained by more insulin resistance and hyperglycaemia as other classical risk factors for CAD like

increased production of ROS, inflammation, dyslipidemia, obesity and elevated blood pressure are result of both of them. Various phenotypic alterations in T2D individuals are associated with endothelial damage and structural changes in arteries. Defect in PI3-Akt pathway and increased production of ROS are the major factors responsible for it and further, enhanced thrombus formation in T2D individuals worsens the scenario. On the genetic front, *TCF7L2* and *PPAR gamma* have emerged as an important candidate genes linking both the conditions as these are the most replicated genes in T2D GWAS among the various populations worldwide, other genes like *Adiponectin, IRS1*, *TNF-alpha*, *ACE*, *Calpain 10*, *IL6*, *IL10, FAB4*, *GST* and *Paraoxonse* have been found to be associated with T2D in various populations with conflicting results. A number of studies have been done for the association of various polymorphisms in these genes with CAD but there is a lack of case control studies in T2D individuals with CAD. In GWAS studies, only one locus on chromosome location 9p21.3 (ANRIL) has been found to link both the conditions.

Lacunae in the genetic studies: There is a lack of the genetic determinants linking T2D and CAD, as both are the heterogeneous disorders with difficulties in determining the phenotypes .As they represent many diseases with a common phenotype, clinically it has been very difficult to distinguish the different categories of the disease. Increased phenotypic heterogeneity can lead to the loss of statistical power. For CAD, different phenotypic criterions have been used for its classification. The difference in criterion for diagnosis results in failure to differentiate between the associated phenotypes and the actual disease. Secondly, most of the GWAS studies were done on European ancestry and only a few GWAS have evaluated the rare alleles responsible for the segment of heritability. A better understanding of the complex mechanisms like (Gene- gene, Gene-environment interaction) would give a clear picture of common variants in T2D and CAD (Sousa *et al,*2011).

CAD is caused by the combined contribution of various metabolic and hormonal factors which often cluster in T2D individuals, but the reason for enhanced susceptibility for CAD among diabetic subjects is still not clear. The molecular mechanisms by which genes of various pathways affect the endothelial function are yet to be clearly elucidated. The complex interaction like Gene-gene, Gene –environment and epigenetic mechanisms further complicate the issue of addressing the link between the two diseases. It has been seen in various studies done on CAD and T2D. Though various authors have studied

CAD and T2D separately in GWAS and candidate gene studies, there is scarcity of studies on CAD in T2D patients across the globe. Thus, Comprehensive studies on CAD patients suffering from T2D are strongly needed to elucidate the relation of T2D and CAD as the prediction of individuals at risk for developing premature atherosclerosis or CAD is important to select patients at high risk for more aggressive intervention strategies at an early stage of T2D.

REFERENCES

1. Abott RD,Donahue RP, Kannel WB,Wilson PW.1988. The impact of diabetes on survival following myocardial infarction in men vs women: the Framingham study. *JAMA* 260:3456-60.
2. Ahima RS, Flier JS.2000. Adipose tissue as an endocrine organ.*Trend Endocrinol Metabol*11 (8): 327–32.
3. Al-Daghri NM, Al-Attas OS, Alokail MS, Alkharfy KM, Hussain T. 2011.Adiponectin gene variants and the risk of coronary artery disease in patients with type 2 diabetes. *Mol Biol Rep* 38(6): 3703-8.
4. Allen RA, Lee EM, Roberts DH, Park BK, Pirmohamed M. 2001. Polymorphisms in the TNF-alpha and TNF-receptor genes in patients with coronary artery disease. *Eur J Clin Invest* 31(10): 843-51.
5. Alsmadi O, Al-Rubeaan K, Mohamed G, Alkayal F, Al-Saud H, Al-Saud NA, Al-Daghri N, Mohammad S, Meyer BF. 2008. Weak or no association of TCF7L2 variants with Type 2 diabetes risk in an Arab population. *BMC Med Genet*. 9: 72.
6. American Diabetes Association.2012. Diagnosis and classification of diabetes mellitus *Diabetes Care* 35 (Suppl 1): S64–S71.
7. Athanassios M, Anastasia T, Antigoni C,Grigorios G, Dimitrios D, Panagiotakos D, Dennis VC.2008. Inflammatory cytokine gene variants in coronary artery disease patients in Greece.*Coron Arter Dis* 19(8): 575-82.
8. Baroni MG, D'Andrea MP., Montali A, Panniteri G, Barilla F, Campagna F, Mazzei E, Lovari S, Seccareccia F, Campa PP, Ricci G, Pozzili P, Urbinati G, Arca M.1999. A common mutation in the insulin receptor substrate-1 gene is a risk factor for coronary artery disease. *Arterioscler Thromb Vasc Biol* 19: 2975-80.
9. Bodhini D, Radha V, Mohan V.2011.Association study of IRS1 gene polymorphisms with type 2 diabetes in South Indians. *Diabetes Technol Ther*13: 767-72.

10. Bonora E.2005. Insulin resistance as an independent risk factor for cardiovascular disease : clinical assessment and therapy approaches. *Av Diabetol* 21: 255-61.
11. Borzyszkowska J, Stanislawska-Sachadyn A, Wirtwein M,Sobiczewski W, Ciecwierz D, Targonski R, Gruchala M, Rynkiewicz A, Limon J. 2012. Angiotensin converting enzyme gene polymorphismis associated with severity of coronary artery disease in men with high total cholesterol levels. *J Appl Genet* 53: 175–82.
12. Broadbent HM, Peden JF, Lorkowski S, Goel A, Ongen H, Green F, Clarke R, Collins R, Franzosi MG, Tognoni G.2008. Susceptibility to coronary artery disease and diabetes is encoded by distinct, tightly linked SNPs in the ANRIL locus on chromosome 9p. *Hum Mol Genet* 17(6):806-14.
13. Burguete Garcia AI, Cruz- lopez M, Madrid- marina, Lopez- Ridaura R, Hernandez-avila M, Cortina B, Gomez RE, Velasco- mondragon E.2010. Association of Gly972Arg polymorphism of IRS1 gene with type 2 diabetes mellitus in lean participants of national health survey in Mexico:a candidate gene study. *Metab clin experiment* 59:38-45.
14. Caballero AE. 2003. Endothelial dysfunction in obesity and insulin resistance: a road to diabetes and heart disease. *Obes Res* 11(11):1278-89.
15. Cauchi S, Meyre D, Dena C,Choquet H, Samson C, Gallina S, Balakau B, Charpentier G, Pattou F, Stetsyuk V, Scharfmann R, Stails B, Fruchbeck G, Froguel P.2006. Transcription factor TCF7L2 genetic study in French population: expression in human beta cells and adipose tissue and strong association with T2D. *Diabetes* 55:2903:08.
16. Ceriello A.2011.Diabetic complications:from oxidative stress to inflammatory cardiovascular disorders. *Medicographia. 33:29-34.*
17. Chandak GR, Janipalli CS, Bhaskar S, Kulkarni SR, Mohankrishna P, Hattersley AT, Frayling TM, Yajnik CS. 2007. Common variants in the TCF7L2 gene are strongly associated with type 2 diabetes mellitus in the Indian population. *Diabetologia* 50(1):63-7.
18. Chang YC, Chang TJ, Jiang YD, Kuo SS, Lee KC, Chiu KC, Chuang LM. 2007. Association study of the genetic polymorphisms of the transcription factor 7-like 2 (TCF7L2) gene and type 2 diabetes in the Chinese population. *Diabetes* 56(10):2631-7.

19. Chiha M, Njeim M, Chedrawy EG.2012.Diabetes and coronary heart disease: a risk factor for the global epidemic. *Int J Hypertens* 2012:1-7.
20. Chiodini BD, Specchia C, Gori F, Barlera S, D'Orazio A, Pietri S, Crociati L, Nicolucci A, Franciosi M, Signorini S. 2010.Adiponectin gene polymorphisms and their effect on the risk of myocardial infarction and type 2 diabetes: an association study in an Italian population. *Ther Adv Cardiovasc Dis* 4(4):223-30.
21. Christiansen T, Richelsen B, Bruun JM .2005. Monocyte chemoattractant protein-1 is produced in isolated adipocytes, associatedwith adiposity and reduced after weight loss in morbid obese subjects.*Int J Obes* 29:146–50.
22. Comuzzie AG, Funahashi T, Sonnenberg G, Martin LJ, Jacob HJ, Black AE, Maas D, Takahashi M, Kihara S, Tanaka S. 2001. The genetic basis of plasma variation in adiponectin, a global endophenotype for obesity and the metabolic syndrome. *J Clin Endocrinol Metab* 86(9):4321-5.
23. Cullen P. 2000. Evidence that triglycerides are an independent coronary heart disease risk factor. *Am J Cardiol* 86:943-49.
24. Deepa R, Arvind K, Mohan V. 2002. Diabetes and risk factors for coronary artery Disease. *Curr Sci* 83(12): 1497-1505.
25. Ding S, Liu L, Zhuge QC, Yu Z, Zhang X, Xie J, Hong W, Wang S, Yang Y, Chen B. 2012.The meta-analysis of the association of PPARG P12A, C161T polymorphism and coronary heart disease. *Wien Klin Wochenschr* 124(19-20):671-77.
26. Donxia l, Qui H, Lisong L, jincheng G.2008. Association of peroxisome proliferator-activated receptor gene Pro12ala and C161T polymorphisms with metabolic syndrome. *Cir J* 72:551-57.
27. D'Souza A, Hussain M, Howarth FC, Woods NM, Bidasee K, Singh J. 2009. Pathogenesis and pathophysiology of accelerated atherosclerosis in the diabetic heart. *Mol Cell Biochem* 331(1-2):89-116.
28. Eckel RH, Kahn SE, Ferrannini E, Goldfine AB, Nathan DM, Schwartz MW, Smith RJ, Smith SR.2011. Obesity and Type 2 Diabetes: what can be unified and what needs to be individualized? *J Clin Endocrinol Metab* 96(6):1654–63.
29. Eckel RH, Wassef M, Sobel B, Barrett E, King G, Lopes- Virella, Reusch J, Ruderman N, Steiner G,Vlassara H. 2002. AHA Conference proceedings Prevention conference VI Diabetes and Cardiovascular disease writing group II: Pathogenesis of Atherosclerosis in Diabetes. *Circulation* 105:e138-e143.

30. Eddy D, Schlessinger L, Kahn R, Peskin B, Schiebinger R. 2009. Relationship of insulin resistance and related metabolic variables to coronary artery disease: a mathematical analysis. *Diabetes Care* 32(2):361-6.
31. Ehses JA, Boni-Schnetzler M, Faulenbach M, Donath MY.2008. Macrophages, cytokines and beta-cell death in Type 2 diabetes. *Biochem Soc Trans* 36(Pt 3):340-2.
32. Elahi MM, Gilmour A, Matata BM, Mastana SS.2008. A variant of position −308 of the Tumour necrosis factor alpha gene promoter and the risk of coronary heart disease.*Heart Lung and Circ* 17:14-18.
33. Elnoamany FM, Dawood AA, Azmy RM, Elnajjar MM.2012. Paraoxonase 1 gene (Gln192-Arg) polymorphism and the risk of coronary artery disease in type 2 diabetes mellitus. *World J Cardiovasc Dis* 2:29-37.
34. Esteghamati A, Mansournia N, Nakhjavani M, Mansournia MA, Nikzamir A, Abbasi M. 2012.Association of +45(T/G) and +276(G/T) polymorphisms in the adiponectin gene with coronary artery disease in a population of Iranian patients with type 2 diabetes. *Mol Biol Rep* 39(4):3791-7.
35. Feg R, Li Y, Zhao D, Wang C, Niu Y, Sun C. 2009. Lack of association between TNF 238 G/A polymorphism and type 2 diabetes: a meta-analysis. *Acta Diabetol* 46(4):339-43.
36. Feng RN, Zhao C, Sun CH, Li Y.2011. Meta-analysis of TNF 308 G/A polymorphism and type 2 diabetes mellitus. *PLoS One* 6(4):e18480.
37. Florez JC, Sjogren M, Burtt N, Orho-Melander M, Schayer S, Sun M, Almgren P, Lindbald U, Tuomi T, Gaudet D, Hudson TJ, Daly MJ, Ardlie KG, Hirschorn JN, Altshuler D and Groop L.2004. Association testing in 9,000 people fails to confirm the association of the Insulin receptor substrate 1 G972R polymorphism with type 2 diabetes. *Diabetes* 53:3313-18.
38. Foucan L, Ezourhi N, Maimaitiming S, Hedreville S, Inamo J, Atallah A, Bangou-Bredent J, Aubert R, Chout R, Fumeron F.2010. Adiponectin multimers and ADIPOQ T45G in coronary artery disease in Caribbean type 2 diabetic subjects of African descent. *Obesity* 18(7):1466-8.
39. Frederiksen L, Brodbaek K, Fenger M, Jorgensen T, Borch-Johnsen K, Madsbad S, Urhammer SA. 2002. Comment: studies of the Pro12Ala polymorphism of the PPAR-gamma gene in the Danish MONICA cohort: homozygosity of the Ala allele confers a decreased risk of the insulin resistance syndrome. *J Clin Endocrinol Metab* 87(8):3989-92.

40. Galgani A, Valdes A,. Erlich HA, Mano C, Cheng S, Petrone A' ,Sentinelli F, Berni A, Baroni MG, Buzzetti R.2010. Homozygosity for the Ala allele of the PPARγ2 Pro12Ala polymorphism is associated with reduced risk of coronary artery disease . *Dis markers* 29 (5):259-64.
41. Giacconi R, Cipriano C, Muti E, Costarelli L, Malavolta M, Caruso C, Lio D, Mocchegiani E.2006.Involvement of -308 TNF-alpha and 1267 Hsp70-2 polymorphisms and zinc status in the susceptibility of coronary artery disease (CAD) in old patients. *Biogerontology* 7(5-6):347-56.
42. Goodarzi MO, Taylor KD, Guo X, Quinones MJ, Cui J, Li Y, Saad MF, Yang H, Hsueh WA, Hodis HN. 2005. Association of the diabetes gene calpain-10 with subclinical atherosclerosis: the Mexican-American Coronary Artery Disease Study. *Diabetes* 54(4):1228-32.
43. Guo T, Hanson RL, Traurig M, Muller YL, Ma L, Mack J, Kobes S, Knowler WC, Bogardus C, Baier LJ. 2007. TCF7L2 is not a major susceptibility gene for type 2 diabetes in Pima Indians: analysis of 3,501 individuals. *Diabetes* 56(12):3082-8.
44. Haffner SM. 2003. Pre-diabetes, insulin resistance, inflammation and CVD risk. *Diabetes Res Clin Pract* 61 Suppl 1:S9-S18.
45. Hajeer AH, Hutchinson IV.2000. TNF-alpha gene polymorphism: clinical and biological implications. *Microsc Res Tech* 50(3):216-28.
46. Heid IM, Wagner SA, Gohlke H, Iglseder B, Mueller JC, Cip P, Ladurner G, Reiter R, Stadlmayr A, Mackevics V and others. 2006. Genetic architecture of the APM1 gene and its influence on adiponectin plasma levels and parameters of the metabolic syndrome in 1,727 healthy Caucasians. *Diabetes* 55(2):375-84.
47. Heiskanen M, Kahonen M, Hurme M, Lehtimaki T, Mononen N, Juonala M, Hutri-Kahonen N, Viikari J, Raitakari O, Hulkkonen J.2010.Polymorphism in the IL10 promoter region and early markers of atherosclerosis: the Cardiovascular Risk in Young Finns Study. *Atherosclerosis* 208(1):190-6.
48. Imen B, Asma O, Jihène R, Lamia R, Nabila BR, Naoufel N, Ahmed BA, Essia B,Ali B.(2011).Single-nucleotide polymorphisms at the adiponectin locus and risk of coronary artery disease in Tunisian coronaries. *J Cardiovasc Med* 12(9):619-24.
49. Jax TH, Peters AJ, Plehn G. Schoebel C.2009. Hemostatic risk factors in patients with coronary artery disease and type 2 diabetes- a two year follow up of 243 patients.*Cardiovas Diabetol* 8:48.

50. Jellema A, Zeegers MP, Feskens EJ, Dagnelie PC, Mensink RP. 2003. Gly972Arg variant in the insulin receptor substrate-1 gene and association with Type 2 diabetes: a meta-analysis of 27 studies. *Diabetol* 46: 990-95.
51. Kadowaki T, Yamauchi T. 2005. Adiponectin and adiponectin receptors. *Endocr Rev* 26(3):439-51.
52. Kawano J, Arora R. 2009. The role of adiponectin in obesity, diabetes, and cardiovascular disease. *J Cardiometab Syndr* 4(1):44-9.
53. Khodeer SA, Abdu-Allah AM, El-Azeem, WFA, Mahfouz RG , Khamis S.2011. Adiponectin Single Nucleotide Polymorphism 45T/G and its Relationship to Adiponectin Level in Egyptian Patients with Type 2 Diabetes Mellitus.*J. Pharm. Biomed. Sci* 1(5) :87-92.
54. Kobayashi T, Matsumoto T and Kamata K. 2005.The PI3-K pathway: roles related to alterations in vasomotor responses in diabetic models. *J Smooth Mus Res*.41: 283-02.
55. Kucharska-Newton AM, Monda KL, Bielinski SJ, Boerwinkle E, Rea TD, Rosamond WD, Pankow JS, Kottgen A, Heiss G, North KE.2010.Role of BMI in the Association of the TCF7L2 rs7903146 Variant with Coronary Heart Disease: The Atherosclerosis Risk in Communities (ARIC) Study. *J Obes*.2010.1-5
56. Laakso M.2010.Cardiovascular disease in type 2 diabetes from population to man to mechanisms: the Kelly West Award Lecture 2008. *Diabetes Care* 33(2):442-9.
57. Lazarevic G, Milojkovic M, Tasic I, Najman S, Antic S, Stefanovic V. 2008. PC-1 (ENPP1) K121Q polymorphism in overweight and obese type 2 diabetic coronary heart disease patients. *Acta Cardiol* 63(3):323-30.
58. Lee YY, Lee NS, Cho YM, Moon MK, Jung HS, Park YJ, Park HJ, Youn BS, Lee HK, Park KS.2005. Genetic association study of adiponectin polymorphisms with risk of Type 2 diabetes mellitus in Korean population. *Diabet Med* 22(5):569-75.
59. Libby P. 2002. Inflammation in atherosclerosis. *Nature* 420(6917):868-74.
60. Liu K, Xu L, Szalkowski D, Li Z, Ding V, Kwei G, Huskey S, Moller DE, Heck JV, Zhang BB and others. 2000. Discovery of a potent, highly selective, and orally efficacious small-molecule activator of the insulin receptor. *J Med Chem.* 43(19):3487-94.
61. Ludovico O, Pellegrini F,Paola RD, Minenna A, Mastroianno S, Cardellini M, Marini MA, Andreozzi F, Vaccaro O, Sesti Gand Trischitta V. 2007. Heterogeneous effect of

Peroxisome proliferator-activated receptor γ2 Ala12 variant on type 2 diabetes risk. *Obesity* 15(5):1076-81.

62. Manfredi S, Calvi D, del Fiandra M, Botto N, Biagini A, Andreassi MG. 2009. Glutathione S-transferase T1- and M1-null genotypes and coronary artery disease risk in patients with Type 2 diabetes mellitus. *Pharmacogenomics* 10(1):29-34.
63. Marchetti P, Coppeli A. Giannarelli R. 2007. Pathophysiological links between diabetes and heart disease. *Medicographia* 29 (3):213-19.
64. Marini MD, Frontoni S, Mineo D, Bracaglia D, Cardellini M, Nicolais PD, Baroni A, D'Alfonso, Perna M, Lauro D, Federici M., Gambardella S, Lauro R, Sesti G.2003. The Arg^{972} variant in insulin receptor substrate-1 is associated with an atherogenic profile in offspring of type 2 diabetic patients. *J clinical endocrinology and metabolism* 88(7):3368-71.
65. Masud R, Qureshi IZ. 2010. Tetra primer ARMS-PCR relates folate/homocysteine pathway genes and*ACE* gene polymorphism with coronary artery disease. *Pathophysiol Nat Hist* 21(3):151-56.
66. Mazzone T.2000.Scavenger receptors in atherosclerosis: new answers, new questions. *Arterosclerosis Thromb vasc Biol* 20:2506-08.
67. McPherson R, Pertsemlidis A, Kavaslar N, Stewart A, Roberts R, Cox DR, Hinds DA, Pennacchio LA, Tybjaerg-Hansen A, Folsom AR and others. 2007. A common allele on chromosome 9 associated with coronary heart disease. *Science.* 316(5830):1488-91.
68. Memisoglu A, Hu FB, Hankinson SE, Liu S, Meigs JB, Altshuler DM, Hunter DJ, Manson JE. 2003. Prospective study of the association between the proline to alanine codon 12 polymorphism in the PPARgamma gene and type 2 diabetes. *Diabetes Care* 26(10):2915-7.
69. Meshkani R, Taghikhani M, Larijani B, Bahrami Y, Khatami S, Khoshbin E, Ghaemi A, Sadeghi S, Mirkhani F, Molapour A, Adeili K.2007. Pro12Ala polymorphism of the peroxisome proliferator-activated receptor-gamma2 (PPARgamma-2) gene is associated with greater insulin sensitivity and decreased risk of type 2 diabetes in an Iranian population. *Clin Chem Lab Med* 45(4):477-82.
70. Mohamed MB, Mtiraoui N, Ezzidi I, Chaieb M, Mahjoub T, Almawi WY.2007. Association of the peroxisome proliferator-activated receptor-gamma2 Pro12Ala but

not the C1431T gene variants with lower body mass index in Type 2 diabetes. *J Endocrinol Invest* 30(11):937-43.

71. Mohammadzadeh G, Zarghami N .2009. Associations between single-nucleotide polymorphisms of the adiponectin gene, serum adiponectin levels and increasedrisk of type 2 diabetes mellitus in Iranian obese individuals. *J of Sc and Clin Lab Invest* 15:1-8.
72. Mohan V, Deepa R, Rani SS, Premlatha G.2001. Prevalence of Coronary artery disease and its relationship to lipids in selected population in south India: The Chennai Urban population Study (CUPS no 5). *J Am college cardiol.* 38 (3):682-87.
73. Mohan V, Deepa R, Velmurugan K, Gokulakrishnan K.2005. Association of small dense LDL with coronary artery diseas and diabetes in urban asian Indians-the Chennai rural Epidemiological Study (CURES8). *J Assoc Physicians India* 53:95-100.
74. Mohan V, Venkataraman JV, Pradeepa R.2010.Epidemiology of cardiovascular disease in type 2 diabetes: The Indian scenario.*J Diabet sci Tech* 4(1): 158-170.
75. Moller DE. 2000. Potential role of TNF-alpha in the pathogenesis of insulin resistance and type 2 diabetes. *Trends Endocrinol Metab* 11(6):212-7.
76. Mori H, Ikegami H, Kawaguchi Y, Seino S, Yokoi N, Takeda J, Inoue I, Seino Y, Yasuda K, Hanafusa T. 2001. The Pro12 -->Ala substitution in PPAR-gamma is associated with resistance to development of diabetes in the general population: possible involvement in impairment of insulin secretion in individuals with type 2 diabetes. *Diabetes* 50(4):891-4.
77. Muendlein A, Saely CH, Geller-Rhomberg S, Sonderegger G, Rein P, Winder T, Beer S, Vonbank A, Drexel H.2011. Single nucleotide polymorphisms of TCF7L2 are linked to diabetic coronary atherosclerosis. *PLoS One* 6(3):e17978.
78. Murdolo G, Smith U. 2006. The dysregulated adipose tissue: a connecting link between insulin resistance , type 2 diabetes mellitus and atherosclerosis. *Nutr Metab Cardiovasc Dis* 16 Suppl 1:S35-8.
79. Nandi A, Kitamura Y, Kahn CR, Accili D.2004.Mouse models of insulin resistance. *Physiol Rev* 84:623– 47.

80. Niu W, Qi Y, Gao P, Zhu D. 2010.Angiotensin converting enzyme D allele is associated with an increased risk of type 2 diabetes: evidence from a meta-analysis. *Endocr J* 57(5):431-8.
81. Osmark P, HannsonO, Jonnson A, Ronn T,Groop L, Renstorm E.2009. Unique splicing pattern of TCF7L2 gene in human pancreatic islets.*Diabetologia* 52:850-54.
82. Phulukdaree A, Khan S, Moodley D, Chuturgoon AA. 2012. GST polymorphisms and early-onset coronary artery disease in young South African Indians. *S Afr Med J* 102(7):627-30.
83. Pickup JC. 2004. Inflammation and activated innate immunity in the pathogenesis of type 2 diabetes. *Diabetes Care* 27(3):813-23.
84. Plutzky J.2004. Inflammation in atherosclerosis and diabetes Mellitus.*Rev Endocrinol Metab* 5:255-59.
85. Qureshi SA, Ding V, Li Z, Szalkowski D, Biazzo-Ashnault DE, Xie D, Saperstein R, Brady E, Huskey S, Shen X. Liu K, Xu L, Salituro GM, Heck JV, Moller DE,Jones AB, Zhang BB. 2000. Activation of insulin signal transduction pathway and anti-diabetic activity of small molecule insulin receptor activators. *J Biol Chem* 275(47):36590-5.
86. Rains JL, Jain SK. 2011.Oxidative stress, insulin signaling, and diabetes. *Free Radic Biol Med* 50(5):567-75.
87. Rees SD, Bellary S, Britten AC, O'Hare JP, Kumar S, Barnett AH, Kelly MA. 2008. Common variants of the TCF7L2 gene are associated with increased risk of type 2 diabetes mellitus in a UK-resident South Asian population. *BMC Med Genet* 9:8
88. Ronald B, Goldberg J.2009. Cytokine and cytokine-like inflammation markers, endothelial dysfunction, and imbalanced coagulationin development of diabetes and Its complications.*Clin Endocrinol Metab* 94(9):3171–82.
89. Sabouri S, Ghayour-Mobarhan M, Moohebati M, Hassani M, Kassaeian J, Tatari F, Mahmoodi-kordi F, Esmaeili HA, Tavallaie S, Paydar R.2011.Association between 45T/G polymorphism of adiponectin gene and coronary artery disease in an Iranian population. *Sci World J* 11:93-101.
90. Sanghera DK, Demirci FY, Been L. 2010. PPARG and ADIPOQ gene polymorphisms increase type 2diabetes mellitus risk in Asian Indian Sikhs: pro12ala still remains a strongest predictor. *Metabolism* 59:492-501.
91. Savoia C, Schiffrin EL. 2007. Vascular inflammation in hypertension and diabetes: molecular mechanisms and therapeutic interventions. *Clin Sci* 112(7):375-84.

92. Sayed-Tabatabaei FA, Oostra BA, Isaacs A, van Duijn CM, Witteman JC. 2006. ACE polymorphisms. *Circ Res* 98(9):1123-33.
93. Semple RK, Krishna V, Chatterjee K, O'Rahilly S. 2006. PPARand human metabolic disease.*J Clin. Invest* 116:581–89.
94. Sesti G, Federici M, Hribal ML, Lauro D, Sbraccia P. Lauro R.2001. Defects of the insulin receptor substrate (IRS) system in human metabolic disorders. *FASEB J* 15:2099-2111.
95. Shafiee SM, Firoozrai M, Salimi S, Zand H, Hesabi B, Mohebbi A.2010. Angiotensin converting enzyme DD genotype not associated with increased risk of coronary artery disease in the Iranian population. *Pathophysiology* 17(3):163-7.
96. Shaw JE, Sicree RA, Zimmet PZ.2010. Global estimates of the prevalence of diabetes for 2010 and 2030.*Diabetes Res Clin Pract* 87:4-14.
97. Sousa A G, Selvatici L, Krieger JE, Pereira AC.2011. Association between genetics of diabetes, coronary artery disease, and macrovascular complications: exploring a common ground hypothesis. *Rev Diabet Stud* 8(2):230-44.
98. Strohmer B, Holzel B, Reiter R, Paulweber B.2005. The g972R polymorphism in the insulin receptor substrate (IRS)-1 gene doesnot correlate with angiographic presence of significant coronary artery disease. *J Clin basic Cardiol* 8:61-64.
99. Szopa M , Malgorzata-Malek M, Wilk B, Skupien J,Wolkow P, Maleki M, Sieradzki J.2008.Variants of adiponectin gene and type 2 diabetes in a Polish population.*Acta Diabetol* 46(4) :317-22 .
100. Tasic I, Milojkovic M, Sunder-Plassmann R, Lazarevic G, Tasic NM, Stefanovic V. 2007. The association of PC-1 (ENPP1) K121Q polymorphism with metabolic syndrome in patients with coronary heart disease. *Clin Chim Acta* 377(1-2):237-42.
101. Tsai CT, Hwang JJ, Lai LP, Chiang FT, Tseng YZ. 2002. IRS-1 Gly971Arg variant is not a new risk factor for coronary artery disease in the Taiwanese population. *Arterioscler Thromb Vasc Biol* 22(1):194.
100. Tuncman G, Erbay E, Hom X, De Vivo I, Campos H, Rimm EB, Hotamisligil GS. 2006.A genetic variant at the fatty acid-binding protein aP2 locus reduces the risk for Hypertriglyceridemia, type 2 diabetes, and cardiovascular disease. *Proc Natl Acad Sci U S A* 103(18):6970-5.
101. Vaisi-Raygani A, Ghaneialvar H, Rahimi Z, Nomani H, Saidi M, Bahrehmand F, Tavilani H, Pourmotabbed T.2010. The angiotensin converting enzyme D allele is an independent risk factor for early onset coronary artery disease. *Clin Biochem*

43(15):1189- 94.

102. White M.F. 2002. IRS proteins and the common path to diabetes. *Am J Physiol Endocrinol Metab* 283: 413-422.

103. Yilmaz- Aydogan H, Kurnaz O, Kurt O, Akadam –teker B , Kucukhuseyin O, Tekeli A, Isbir T.2011. Effects of the PPARG P12 A and C1431T gene variants on serum lipid profile in coronary heart disease patients with and without type 2 diabetes. *Mol Cell biochem* 358:355-363.

104. Yoo WS, Kim HJ,Kim D,Lee MY,Chung HK.2009.Early detection of asymptomatic coronary artery disease in patients with type2 diabetes mellitus. *Kor J int med* 4(3):183-189

105. Zhang HF, Xie SL, Wang JF, Chen YX, Wang Y, Huang TC.2011. Tumor necrosis factor- alpha G-308A gene polymorphism and coronary heart disease susceptibility:an updated meta-analysis. *Thromb Res* 127(5):400-5.

106. Zhou A,Chen J, Xu W. 2011. Association between C1431T polymorphism in peroxisome proliferator-activated receptor-γ gene and coronary artery disease in chinese han population. *Mol bio Rep* 39:1863-1868.

107. Zhou JB, Yang JK, Lu JK, An YH.2010.Angiotensin-converting enzyme gene polymorphism is associated with type 2 diabetes: a meta-analysis. *Mol Biol Rep* 37(1):67-73.

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