Type 2 Diabetes Mellitus: Impact of genetics and environment


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Abstract

Type 2 diabetes (T2D) develops while the body can still produce insulin, but not enough, or when the insulin produced doesn’t work properly. It has become a health-care problem worldwide, with the raise in disease prevalence being all the more worrying as it not only affects the developed world but also developing nations with fewer resources to cope with yet another major disease burden. Furthermore, the problem is no longer restricted to the ageing population, such as young adults and children are also being diagnosed with T2D. Genes play an important role in the development of diabetes mellitus. Type 2 diabetes is a polygenic disorder with multiple genes located on different chromosomes contributing to its susceptibility, including TCF7L2, KCNJ11, PPARG, ENPP1, Adiponectin, Calpain 10, PTPN1, CDKAL1, ABCC8, HNF4A, SLC2A2, UCP2, INS, PIK3RI and SOS1 gene. The environmental factor (arsenic, pesticides, selenium, bisphenol A, phthalates and microorganism) also associated with Type 2 diabetes. Researchers found that taking proper exercise, vaccination against causing enterovirous, regulation of taking diet and keep away from smoking are the best away prevent from type 2 diabetes. This review aims to provide the link of causative factor to develop type 2 diabetes and search the possible away of prevention against type 2 diabetes.

Keywords: Type 2 diabetes, insulin resistance, gene, environmental factor

Introduction

Diabetes mellitus type 2 also known as noninsulin-dependent diabetes mellitus (NIDDM) or adult-onset diabetes is a metabolic disorder that is characterized by high blood glucose level in the context of insulin resistance and relative insulin deficiency (Vinay et al., 2005). Insulin resistance is a term that describes the reduced ability for cells to store away blood sugar. In essence, the hormone insulin, which activates the blood sugar storage process, becomes increasingly ineffective.

Type 2 Diabetes has a complex pathogenesis that was classically characterized by pancreatic β-cell dysfunction followed by decrease of the beta cell mass, peripheral insulin resistance and raised hepatic glucose production. β-cell dysfunction is occurred initially by diminished firstphase insulin response after glucose stimulation but also following stimulation with nonglucose secretagogues such as the incretin hormone glucagon-like peptide-1 (GLP-1) (Guja et al., 2012). This type of diabetes is in contrast to diabetes mellitus type 1 where causes an absolute insulin deficiency due to destruction of islet cells in the pancreas. Type 2 diabetes makes up about 90% of cases of diabetes with the other 10% due...
primarily to diabetes mellitus type 1 and gestational diabetes. Obesity is thought to be the primary cause of type 2 diabetes in people who are genetically predisposed to the disease. Rates of type 2 diabetes have elevated markedly over the last 50 years. As of 2010 there are approximately 285 million people with the disease compared to around 30 million in 1985 (Smyth and Heron, 2006). Long-term complications from high blood sugar can result in heart disease, strokes, diabetic retinopathy where eyesight is affected, kidney failure which may require dialysis, and poor circulation of limbs leading to amputations. Diabetes mellitus affects people of every age, race, and background, and is now a major modern cause of premature death in many countries around the world, with someone dying from Diabetes Type 2 every 10 seconds worldwide (Gillespie, 2008).

Genetic factor

Type 2 diabetes is a polygenic disease that different kinds of genes are involved to its expression. On the basis of locus or combination of loci, it may be dominant, recessive, or between of them. Though the identifying of a complex disease is challenging but different strategies have been used in efforts to identify type 2 diabetes susceptibility genes.

TCF7L2 gene

In 2003, a modest peak of linkage was described on chromosome 10 by researchers at deCODE genetics consortium on Icelandic T2D families. The exploration of this linkage signal led to the identification of a T2D associated gene (Grant et al., 2006), namely the gene encoding the Transcription Factor 7-Like 2 (TCF7L2) located at 10q25.3. TCF7L2 (also known as TCF-4) is a transcriptional factor involved in Wnt signaling, being able to bind b-catenin. This pathway of signaling is connected in embryogenesis, including adipocyte and pancreatic tissue formation. A strong association between type 2 diabetes and variation in the transcription factor 7-like 2 (TCF7L2) gene found in Icelandic, Danish, and American populations (Grant et al., 2006). Some studies confirmed TCF7L2 as the locus that confers the strongest responsible on T2D diabetes risk, so that some authors even stated that this could be the biggest story in diabetes genetics since the discovery of HLA’s in T1D (Zeggini and McCarthy, 2007). The physiological implication of this transcription factor is responsible in glucose homeostasis. It has been suggested that intestinal proglucagon gene expression may be regulated by the Wnt/TCF7L2 pathway in enteroendocrine cells (Yi et al., 2005). Thus, TCF7L2 variants may modify type 2 diabetes susceptibility through modulation of glucagon-like peptide-1 (GLP-1) secretion. As for the molecular mechanism of TCF7L2 involvement in T2D pathogenesis, where found that the risk allele leads to impaired insulin secretion by altering three different mechanisms: glucose-stimulated insulin secretion, incretinstimulated insulin secretion and proinsulin-toinsulin conversion (Schafer et al., 2011).

PPARG gene

PPARG gene on chromosome 3in locus 3p25 was an attractive candidate gene because it encodes the molecular target for thiazolidinediones. In 1997, Yen et al. described an association between the proline-to-alanine change at position 12 of PPARG (Pro12Ala or rs1801282) in and the risk of T2D (Guja et al., 2012). A common missense variant in the g2 isoform of peroxisome proliferator–activated receptor gamma, a protein of PPARG gene (PPAR g) [Pro12 to Ala12 (Pro12Ala)] has shown to association with diabetes in
multiple studies, where a meta-analysis suggesting that the common allele is associated with an increased diabetes risk of 25% (Altshuler et al., 2000). A major missense mutations in this gene result in severe, dominantly inherited insulin resistance, diabetes mellitus, and additional features such as partial lipodystrophy and hypertension (Barroso et al., 1999).

**KCNJ11 gene**

The **KCNJ11** gene, located on the short arm of chromosome 11p15.1, encodes the pore-forming subunit of the ATP-sensitive potassium channel Kir6.2 of the pancreatic β-cells. The ATP-sensitive potassium channel which plays a key role in regulating the release of hormones, such as insulin and glucagon, in the beta cell. Gain-of-function mutations of **KCNJ11** open the potassium channel and inhibit the depolarization of β-cells, leading to a defect in insulin secretion (Gloyn et al., 2004). Remarkably, this gene was reported to be involved in the pathogenesis of neonatal diabetes. A missense Glu23Lys mutation was described (E23K or rs5210) in which Glutamate is changed into Lysine at codon 23 of **KCNJ11**. Studies in various populations have consistently reported that substitution of lysine for glutamic acid at the 23rd amino acid (E23K) is associated with an increased risk of T2DM (Florez et al., 2004; Nielsenb et al., 2003). In recent reports of large-scale association studies and meta-analyses, the E23K variation was found to raise the risk of T2DM with an OR of 1.15 (Florez et al., 2006).

**ENPP1 gene**

The gene ectonucleotide pyrophosphatase phosphodiesterase 1 (**ENPP1**), also known as plasma cell glycoprotein 1, which recently found to be associated with both childhood and adult obesity in a French population. A moderate excess of the risk haplotype was also observed in adults with T2DM compared with controls (10.7% vs 7.1%, OR 1.44), and this association was also replicated in an Austrian cohort with similar frequencies. The study of Mantel-Haenszel of 2,569 European subjects supported the association, with OR 1.56 and p=0.00002 (Meyre et al., 2005). The nonsynonymous variant lysine 212 to glutamine (K121Q) has been best studied, and also shown to be associated with obesity but not diabetes in Caucasian and African American subjects ascertained from the New York Cancer Project (Matsuoka et al., 2005). Other researchers also found a connection of K121Q with earlier T2DM onset and coronary disease among T2DM patients (Bacci et al., 2005). The association of K121Q with T2DM was replicated in three relatively small populations among them two of South Asian ancestry and one Caucasian (Abate et al., 2005). Although the K121Q variant appears to associate with T2DM and obesity, additional work is needed to determine the magnitude of the risk. In 2001, Hegele et al. described a K121Q SNP of ENPP1 gene that was strongly associated with insulin resistant. Though different studies on this gene reported a positive association with type 2 diabetes but other well-powered studies failed to replicate this association (Florez, 2008). However, a recent metaanalysis of about 42,000 samples (McAteer et al., 2008) confirmed the association of this ENPP1 gene variant with T2D in European populations under a recessive model (OR 1.38, p < 0.005).

**Calpain 10 gene**

The first common diabetes gene report of a positive result emerging from GWL scanning in T2D families was represented by **CAPN-10** (region of chromosome 2),...
the gene encoding Calpain 10. CAPN10 encodes an intracellular calcium-dependent cysteine protease that is ubiquitously expressed in both adult and fetal tissues (Cox et al., 2004). A haplotype that was initially linked to T2D included an intronic A to G mutation at position 43, which shows to be involved in CAPN10 transcription. In 2000, Horikawa et al. reported three single nucleotide polymorphisms (SNPs) in the CAPN-10 gene associated with T2D: SNP-43 (G/A) in intron 3, SNP -19 (3/2) in intron 6 and SNP-63 (C/T) in intron 13 and described several T2D associated haplotypes. Though the exact mechanism of CAPN-10 gene involvement in T2D pathogenesis remains unknown but functional evidence accumulated in recent studies suggests a potential role in both insulin resistance and insulin secretion (Turner et al., 2005).

Adiponectin gene

In 2000, a GWL study on French families identified a peak of linkage on chromosome 3q27-pter (Vionnet et al., 2000) and it was shown to segregate with T2D and MetS on chromosome 3q27 in both French and Japanese populations. A strong linkage was found this gene in Hispanic Americans by the Insulin Resistance and Atherosclerosis Study Family Study (Guo et al., 2006) but not confirmed in Pima Indians and African Americans (Grigorescu et al., 2011). Adiponectin (ApN or ADPN or ADIPOQ or APM1) is a 30 kDa protein structurally similar to complement 1q, secreted by adipocytes. ApN plays an important role in insulin action, energy homeostasis, inflammation etc. ApN levels are declined in insulin-resistant patients with obesity, T2D or MetS and correlate well with insulin sensitivity. Adiponectin levels correlate negatively with glucose, insulin and triglyceride levels as well as the body mass index (BMI), while there is a positive correlation with high-density lipoproteins (HDL), cholesterol level. SNPs of APM1, the gene encoding adiponectin, were associated with the development of hyperglycemia (Dedoussis et al., 2007). More than 10 SNPs were described in the ADIPOQ gene with possible correlation to the plasma ApN levels, MetS and risk to develop T2D, the best studied being SNP-45 in exon 2 and SNP 276 in intron 2. For SNP-45T/G, the G allele would be pathogenic in most studies and associated to high risk of T2D and reduced insulin sensitivity (Tso et al., 2006). In the French population, two other SNPs (C–11377G and G-11391A) from the promoter region were reported to be associated with hypoadiponectemia and T2D (Vasseur et al., 2002).

PTPN1 gene

The PTPN1 gene ubiquitously expressed protein tyrosine phosphatase-1B (PTP1B), catalyzes the dephosphorylation of tyrosine residues from the insulin receptor kinase activation segment (Seely et al., 1996) and IRS1 (Goldstein et al., 2000) resulting in the down-regulation of insulin signaling. PTP1B also shows negative control on leptin signaling through the dephosphorylation of JAK2 and STAT3 (Cheng et al., 2002). The disruption of the PTPN1 gene in mice results in elevated insulin sensitivity and in resistance to diet-induced obesity (Elchebly et al., 1999), as well as enabling normalization of blood glucose levels. Several studies have investigated the association of T2DM with genetic variants of PTPN1. When analyzing the PTPN1 gene locus, Bento et al. (2004) discovered convincing associations between multiple SNPs and T2DM in two independent Caucasian American case-control samples. Recently published data indicate that PTPN1 variants
might modify the lipid profile, thereby influencing susceptibility to the metabolic syndrome (Cheyssac et al., 2006).

**CDKAL1 gene**

The results of the first T2D genome-wide association studies (GWAS) were published in 2007 in *Nature, Nature Genetics* and *Science* and reported CDKAL1 gene associated with T2D. *CDKAL1* encodes CDK5 regulatory subunit-associated protein 1-like 1 (Steinthorsdottir et al., 2007), which is thought to inhibit cyclin-dependent kinase 5 (CDK5) activity by binding to the CDK5 activator p35. A genetic variation located in 6p22.3 of the *CDKAL1* gene was discovered to be significantly associated with T2DM through the deCODE study (Steinthorsdottir et al., 2007). *CDKAL1* gene also encodes a 579-residue, 65-kD protein sharing considerable amino acid homology with CDK5RAP1, an inhibitor of CDK5 activation and is expressed in human pancreatic islet and skeletal muscle. In a recent study, revealed that disruption of *CDKAL1* in mouse β-cells resulted in impaired first-phase insulin secretion (Ohara-Imaizumi et al., 2010). The people who had risk variants of *CDKAL1* had decreased insulin secretion capacity.

**HNF4A (hepatocyte nuclear factor 4-a)**

Mutations in promoter and coding regions of the *HNF4A* gene cause MODY1. *HNF4A* encodes an orphan hormone nuclear receptor that, together with *TCF1* (LocusLink ID 6927), encoding HNF1α, *TCF2* (LocusLink ID 6928), encoding HNF1β, and *FOXA2* (LocusLink ID 3170), encoding HNF3β, constitutes part of a network of transcription factors regulating gene expression in pancreatic β-cells, liver, and other tissues. These transcription factors control expression of the insulin gene as well as genes encoding proteins associated in glucose transport and metabolism and in mitochondrial metabolism, all of which are linked to insulin secretion in β-cells (Fajans et al., 2001). *HNF4A* maps to Chromosome 20 (Argyrokastritis et al., 1997) in a region that has been connected to Type 2 diabetes in multiple studies (Klupa et al., 2000; Permutt et al., 2001). This positional information, combined with the known role of major mutations at this gene in the causation of autosomal-dominant maturity-onset diabetes of the young (MODY), has led to *HNF4A* being thought as a strong candidate for involvement in causing Type 2 diabetes. The heterozygous nonsense and missense mutations in HNF4a lead to an insulinoaenic form of MODY strongly believes that β-cell dysfunction is sensitive to the amount of HNF4α in the β-cell and that haploinsufficiency is the likely mode of molecular pathogenesis in that condition (Barroso et al., 2003).

**ABCC8 (ATP binding cassette, subfamily C, member 8)**

The *ABCC8* gene is located on chromosome 11p15.1 and several gene variants of both genes have been associated with disorders of insulin secretion and T2DM (Dedoussis et al., 2007). *ABCC8* encodes an ATP-sensitive potassium channel, which plays a key role in regulating the release of hormones, such as insulin and glucagon, in the beta cell. Mutations in either gene can affect the potassium 7 channel’s activity and insulin secretion, ultimately leading to the development of T2D. *ABCC8* variants have been associated with Type 2 diabetes which is shown in multiple studies (Barroso et al., 2003). *ABCC8* (Ala) genes have been associated with T2D, as well as other diabetes-related traits. Because of the close proximity of these gene, current studies are evaluating whether this gene work in concert with each other, or rather have an independent effect on
More recently Florez and colleagues (2004) investigated the ABCC8 gene and tested sufficient variants to completely tag all variation in this region. After that the E23K variant was associated with T2DM in 3,413 subjects, and the association was confirmed in a meta-analysis that contained over 5000 T2DM subjects and 4747 controls (p<10\(^{-5}\), OR 1.15). The E23K variant is in nearly complete linkage disequilibrium (completely correlated) with a Serine to Alanine change at position 1369 in exon 33 of the sulfonylurea receptor, and thus S1369A and E23K cannot be distinguished genetically (Das and Elbein, 2006).

**Jack Spratt gene (new diabetes Gene identified)**

It has long been hypothesized that type 2 diabetes in lean people is more genetically driven. A new study found from a research team which was led by the Peninsula College of Medicine and Dentistry (PCMD), University of Exeter. This research institutions from around the world, has for the first time proved that lean type 2 diabetes patients have a larger genetic disposition to the disease than their obese counterparts. Their study has also identified a new genetic factor associated only with lean diabetes sufferers. The study is published in *PLoS Genetics*. Using genetic data from genome-wide association studies, the research team tested genetic markers across the genome in approximately 5,000 lean patients with type 2 diabetes 13,000 obese patients with the disease and 75,000 healthy controls. The team revealed differences in genetic enrichment between lean and obese cases which support the hypothesis that lean diabetes sufferer have a greater genetic predisposition to the disease. This is in contrast to obese patients with type 2 diabetes, where factors other than type 2 diabetes genes are more likely to be responsible. In addition, genetic variants near the gene, LAMA1 were linked to type 2 diabetes risk for the first time, with an effect that appeared only in the lean patients (Perry et al., 2012).

**SLC2A2 (encoding GLUT2)**

SLC2A2 encodes the glucose transporter GLUT2, a member of the facilitative glucose transporter family that is highly expressed in pancreatic β-cells and liver. It is a highly plausible candidate gene for Type 2 diabetes, as it is a high K\(_m\) transporter that regulates entry of glucose into the pancreatic β-cell. This initiating the cascade of events, leading to insulin secretion. GLUT2 is also highly expressed in the liver, where it is associated in the regulation of both glucose uptake and output. It is notable that the alleles that associated with increased diabetes risk were also all linked with lower fasting insulin levels, suggesting that these may influence basal insulin secretion. In 2003, Barroso et al. typed six SNPs in SLC2A2, three of which SNP21, SNP23, and SNP24 and found significantly associated with diabetes status with an OR of approximately 1.4-1.5. In the QT study, all three disease-associated SNPs were also associated with lower levels of fasting plasma insulin. Rather surprisingly allele 2 (A) at T198, which was connected with increased disease risk, was associated with lower 2-h plasma glucose. No other significant associations with intermediate phenotypes were found (Barroso et al., 2003).

**UCP2 gene**

UCP2 gene located on chromosome 11q13 (SNP, rs659366). It is responsible for impaired insulin secretion that has been shown to predominate over insulin resistance in individuals with early onset T2D. The UCP2 variant has a strong predictor of T2D with earlier onset. The promoter variant in the UCP2 gene has been
associated with increased expression of the gene in adipose tissue. If this variant is associated with increased UCP2 mRNA levels in human pancreatic β-cells (which is not known), this could result in increased uncoupling and, in turn, in decreased formation of ATP and impaired insulin secretion. In 2005, Lyssenko et al. revealed that fifty-eight (44.3%) of the converters were homozygous for the risk genotype (GG) of the UCP2 −866G>A variant and this GG genotype was associated with a modestly increased risk of T2D (HR 1.4, \( p = 0.049 \)). Though this risk was not influenced by BMI and FPG at baseline whereas the GG genotype was also associated with increased risk of developing T2D in patients with earlier onset of diabetes (HR 2.0, 95% CI 1.2–3.3, \( p = 0.0057 \)).

**INS (encoding insulin)**

The INS (LocusLink ID 3630) gene encodes the hormone preproinsulin, which upon proteolytic cleavage creates mature insulin and C-peptide. Barroso et al. (2003) tested a single SNP in the 3′-UTR (SNP72) of the insulin gene (INS) with disease status and found this SNP, significantly associated with increased Type 2 diabetes risk under a recessive model for the T allele (OR 2.02, \( p = 0.0258 \)). The insulin gene variable number tandem repeat (INS–VNTR) has been extensively studied and is proposed to exert pleiotropic effects on birth weight and diabetes susceptibility (Huxtable et al., 2000). The data for the single SNP Barroso et al. (2003) tested suggest that either the insulin gene or other loci in LD may be involved in Type 2 diabetes risk.

**PIK3R1 and SOS1 gene:** The gene PIK3R1, encoding the p85α regulatory subunit of the phosphatidylinositol 3-kinase which is a logical candidate gene for involvement in causing of Type 2 diabetes owing to its role in insulin signal transduction. An intronic variant, SNP42, was associated with increased disease risk under two genetic models (OR 1.41, \( p = 0.0090 \) for the allele 2 dominant and OR1.34, \( p = 0.0088 \) for the additive model (Barroso et al., 2003). According to QT study, Barroso et al. (2003) revealed that SNP42 was significantly associated with increased BMI and showed a borderline significance with increased fasting insulin (measure of insulin resistance) under a dominant model for allele 2. Obesity is a major risk factor for insulin resistance, and the observed increase in BMI coupled with increased insulin resistance in carriers of allele G at SNP42 suggests that variation at this gene may be increasing Type 2 diabetes risk through impaired insulin action.

One study did describe an association with disease status and with QTs underlying Type 2 diabetes (Baier et al., 1998). Finally Barroso et al. (2003) suggested about their research data that variation in this gene is a risk factor for the development of Type 2 diabetes. The gene SOS1 (son of sevenless homolog 1 in Drosophila) encodes a guanine nucleotide exchange factor that performs in the transduction of signals that control cell growth and differentiation. Barroso et al. (2003) analysed two SNPs for association with disease status, a nonsynonymous SNP (N1011S) and an intronic variant (SNP8). While the nonsynonymous S1011 variant, which was very rare (minor allele, 0.003), did not associate with disease status, the intronic SNP was highly significantly associated with decreased disease risk (OR 0.58, \( p = 0.0032 \)). After their study, Barroso et al. (2003) noted that this was the first investigation into the role of SOS1 in Type 2 diabetes risk.

**Environmental factor: Arsenic:** Arsenic can be found naturally in drinking water. Studies of people exposed to
high levels of arsenic from Taiwan, Bangladesh, Mexico, and Sweden have found that arsenic may contribute to the development of diabetes (Coronado-Gonzalez, 2007). Arsenic could influence type 1 diabetes development by mechanisms involving oxidative stress, inflammation, or programmed cell death (apoptosis) (Navas-Acien et al., 2006). Rat pancreatic beta cells treated with arsenic showed impaired insulin secretion and function (Diaz-Villaseñor et al., 2006). A recent study published in the Journal of the American Medical Association (JAMA) revealed that even at lower levels, arsenic exposure was associated with increased prevalence of diabetes in U.S. adults (Navas-Acien et al., 2008). A study from Korea did find an association between arsenic exposure and diabetes in people exposed to normal, background exposure levels of arsenic, especially women (Kim and Lee, 2011). Another newer study found that in people from rural communities in the US with high rates of diabetes, arsenic was associated with poorer diabetes control (a higher HbA1c) in people with. A study from parts of Mexico with historically high levels of arsenic exposure noticed that people who had certain genes are more likely to develop diabetes when exposed to arsenic (Drobona et al., 2012).

**Pesticides**

Pesticides include a number of substances, including herbicides and insecticides. The women who reported agricultural exposure during pregnancy, the risk of diabetes was associated with the use of four herbicides (2,4,5-T; 2,4,5-TP; atrazine; butylate) and three insecticides (diazinon; phorate; carbofuran) (Saldana et al., 2007). Some pesticides can interfere with beta cell function in ways that may promote diabetes development. For an example, atrazine was found to induce obesity and insulin resistance in rats by impairing the function of mitochondria (Lim et al., 2009). Mitochondria dysfunction may be involved in the development of both type 1 and type 2 diabetes (Szabadkai and Duchen, 2009). A study of the staff of an Australian insecticide application program found higher mortality rates for diabetes (probably type 2), as compared with the general Australian population (Beard et al., 2003). The widely-used organophosphate pesticides (including malathion, diazinon, parathion, and chlorpyrifos) have been found to be toxic to the immune system in animals and sometimes humans (Galloway and Handy, 2003). Early life exposure to these pesticides also causes metabolic dysfunction resembling pre-diabetes in animals, especially when adults eat a high-fat diet (Slotkin, 2011). If animals exposed to malathion develop high blood sugar levels, and their carbohydrate metabolism is affected in ways that could increase insulin resistance (Rezg et al., 2010).

**Selenium**

Selenium is an essential trace element, but it can also be toxic at high doses. Selenium has bioaccumulated to four times the toxic level in the food chain, a level that can cause harm in fish and birds. Groundwater wells are also affected, and state advisories are in effect for consumption of fish due to high selenium levels (Palmer et al., 2010). Selenium has been found to associate with type 2 diabetes in some studies of people in the U.S. Laclaustra et al. (2009) revealed that in U.S. adults exposed to background selenium levels, the prevalence of diabetes raised with raising levels of selenium. Fasting glucose levels and hemoglobin A1C levels increased with increasing selenium levels as well. Another study using the same dataset but from an
earlier time period also found selenium levels to be associated with diabetes (Bleys et al., 2007). The dataset used in these studies does not differentiate between type 1 and type 2 diabetes, although most participants would have had type 2.

**Bisphenol A**

It is found that plastic such as water bottles, metal can linings, dental sealants, toys, and other products, and can leach out of these products, especially when exposed to heat or acidity (Welshons et al., 2006). Worldwide, over 6 billion pounds of BPA are produced each year, and over 100 tons are released into the air annually (Vandenberg et al., 2009). A human study has found an association between BPA exposure and increased insulin resistance, general obesity, and abdominal obesity in Chinese adults (Wang et al., 2011). Nadal et al. (2009) expressed how BPA targets the insulin-producing beta cells in the pancreas, and creates insulin resistance in animals. By doing so, it may contribute to beta cell exhaustion. More recent study revealed from the same laboratory confirms these effects, in human beta cells as well as mouse beta cells (Soriano et al., 2012). A further study finds that BPA slows down whole-body metabolism in mice and induces insulin resistance throughout their bodies (Batista et al., 2012).

**Phthalates**

Phthalates are widely used chemicals that soften PVC plastic, and are also used in cosmetics, perfumes, and industrial paints and solvents. Phthalates activate certain hormone receptors called PPARs. PPARs are known to influence blood glucose levels, via insulin resistance, insulin secretion, and fat formation. When pregnant and lactating rats were given DEHP, their offspring formed abnormal beta cells, and alternations of the genes controlling beta cell function at the time of weaning. These results propose that developmental exposure to phthalates can lead to beta cell dysfunction and glucose abnormalities, and is a potential risk factor for diabetes development (Lin et al., 2011). In New York City children, certain phthalate exposures measured at age 6-8 were associated with a higher body mass index and waist circumference one year later (Teitelbaum et al., 2012). Another study on Swedish women, the phthalate MiBP was related to increased abdominal body fat two years later (Lind et al., 2012).

**Gut microbiota**

Gut microbiota may be involved in the development of obesity and type 2 diabetes as well (Cani and Delzenne, 2010). Animal studies find that gut microbiota can affect the formation of obesity, insulin resistance, and diabetes through a variety of mechanisms. A Western diet can raise microbiota that promotes obesity, as could overuse of antibiotics (Musso et al., 2010). In a study of rats, the animals given probiotics had a lower body weight and more diverse intestinal biota than the controls and those who received E coli (a harmful microorganism) (Karlsson et al., 2011). It is especially curious that gastric bypass surgery often leads to lessening of type 2 diabetes without causing any weight loss (Pournaras et al., 2010).

**Prevention from type 2 diabetes**

**Exercise**

Exercise is very important in the control of type 2 diabetes. Obesity is associated with hepatic and peripheral insulin resistance and may have a deleterious influence on the regulation of glucose homeostasis (Coker et al., 2009). Weight gain, especially with central fat accumulation, as indicated by a high waist...
circumference is associated with impaired glucose tolerance (IGT) and type 2 diabetes. Obesity in persons with diabetes is also associated with poorer control of blood glucose levels, blood pressure and cholesterol (Anderson et al., 2003). Increased physical activity and improved diet can delay or even prevent the progression of insulin insensitivity from IGT to overt type 2 diabetes. Insulin resistance is an important pre-cursor to type 2 diabetes, and in its early stages is reversible by weight loss and an increase in physical activity (Ross et al., 2000). The metabolic abnormalities of established type 2 diabetes, including hyperglycaemia, hyperinsulinaemia and dyslipidaemia can be improved by an increase in physical activity. Regular taking of exercise reduce the risk of obesity and thereby minimize the incidence of causing of diabetes types diseases. By losing of weight and increasing physical activity can neutralize the powerful effect of insulin resistance on progression to diabetes (Hossain and Khatun, 2013). A person who takes regular physical exercise appears to: firstly reduce the activity of the pancreatic β-cells and makes cellular tissues more sensitive to insulin, secondly increase the rate at which glucose is taken into the muscles, independent of the activity of insulin and finally improve cardiovascular health and aids weight management (Goodyear and Kahn, 1998).

Keep way from smoking

Smoking has been shown to increase insulin resistance and diminish insulin secretion, both of which are connected with the onset type 1 diabetes. There is a growing body of evidence to show that smoking is a risk factor for Type 2 Diabetes (Yeh et al., 2010). Smoking has been identified as a possible risk factor for insulin resistance, a precursor for diabetes. Smoking has also been shown to deteriorate glucose metabolism which may lead to the onset of type 2 diabetes (Fagard and Nilsson, 2009). In 2010, Yeh et al. conducted a community-based study of 15 792 middle-aged adults, to test the hypothesis that although smoking is an independent predictor of incident type 2 diabetes, smoking cessation increases diabetes risk in the short term, possibly because of cessation-related weight gain. There is also some evidence which suggests that smoking increases diabetes risk through a body mass index independent mechanism. Smoking has been connected with a risk of chronic pancreatitis and pancreatic cancer, suggesting that tobacco smoke may be toxic to the pancreas. A systematic review of 25 studies found that all but one revealed an association between active smoking and an increased risk of diabetes (Willi et al., 2007). On the basis of this review, it is estimated that 12% of all type 2 diabetes in the United States may be attributable to smoking (Ding and Hu, 2007). If the same proportion is applied to the UK, smoking may account for as many as 360,000 cases of diabetes. So, keep way from smoking, is the best away to prevent from type 2 diabetes.

Conclusion

Type 2 diabetes risk is mainly depending upon a genetic susceptibility and environmental factor that make the insulin resistance. Some researches have suggested that taking proper physical exercise to reduce over body weight and maintain proper nutritional diet may also contribute to prevent diabetes. Though the genetic therapy are not well established yet we hope, in the near future scientist can know the roles of these causative genes and their molecular pathways that are related to the risk of T2D and may potentially lead to targeted therapies
for type 2 diabetes patient for treating or preventing diabetes.

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