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# An Overview of Factors Leading to Insulin Resistance

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## Abstract

Diabetes is a health scare across the world especially amongst the elderly. Type 2 diabetes (T2DM), which is a late-onset disease, is the leading cause of kidney failure in Europe and the United States. It also increases a person's risk of cardiovascular disease and nephropathy. Inflammation and oxidative stress increase diabetic complications. Unlike type 1 diabetes which is insulin-dependent and is marked by lack of insulin synthesis, type 2 diabetes is non-insulin dependent and is characterized by insulin resistance. This involves lack of responsivity to insulin despite its abundance in the body. Here we give a brief account of the physiological aspects leading to insulin resistance first and eventually diabetes. Besides, the diagnostic approach is discussed along with useful preventive measures. This paper focuses on genetic and non-genetic factors contributing to insulin resistance in man and also discusses the possible mechanisms involved in disease progression.

***Keywords:*** Type 2 diabetes mellitus, Insulin resistance, cardiovascular disease, nephropathy

## Introduction:

Diabetes is a disease involving elevated blood glucose levels (hyperglycemia) due to impairment of carbohydrate metabolism. It was discovered only around 1935 that the disease has two distinct classes with different clinical presentation (Das & Shah, 2011). The disease is broadly classified into two categories – (i) Type 1 diabetes mellitus (T1DM) or insulin dependent diabetes mellitus (IDDM) and (ii) Type 2 diabetes mellitus (T2DM) or noninsulin Dependent diabetes mellitus (NIDDM). The prevalence of type 2 diabetes is much higher (>80 %) compared to type 1 diabetes (5-10 %). Type 2 diabetes affects around 382 million people worldwide, or 8.3% of the global population. Unlike type 1 diabetes which results from the inability of pancreatic islets of

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Langerhans to secrete insulin, the type 2 diabetes is characterized by normal or even elevated insulin levels but there is lack of responsivity towards insulin. In normal individuals, pancreatic β-cells secrete a basal level of insulin (0.25-1.5 units/hr) during fasting. Most of this insulin (60 %) is removed by the liver so that its concentration in peripheral circulation drops down to 18-90 pmol/L in fasting state (Kahn et al., 1997). The secretion of insulin from the pancreatic islets is also reported to be pulsatile and follows an ultradian rhythm (Pørksen et al., 2002). Insulin then regulates the uptake of glucose by cells such that it remains the preferred source of energy for cells. Insulin binds to receptors on its target cells in the body in order to elicit its physiological effects. The inability of cells to bind insulin is called insulin resistance and is the starting point for prediabetes involving higher than normal glucose levels in the blood. Prediabetes is the precursor for type 2 diabetes which by definition involves persistently elevated glucose both in fasting as well as postprandial state. The progression of the disease is gradual and can be accelerated by a number of factors. Besides, the disease itself has a role in the development of several secondary complications. This happens because in the wake of the inability of cells to metabolize glucose, the body starts depleting stored glycogen and fat reserves to form glucose. Breakdown of excess fatty acids leads to accumulation of ketone bodies (ketosis). Dietary factors such as obesity, smoking, and lack of exercise have all been linked to an increased risk of cardiovascular disease and death in people with type 2 diabetes in developed nations. There is also a strong genetic and environmental basis of type 2 diabetes (Murea et al., 2012) the details of which are being discovered only recently. A number of studies on epigenetic mechanisms may shed light on certain aspects of regulation of genes controlling sugar metabolism. This necessitates a review of our current understanding of insulin resistance and type 2 diabetes in the light of recent developments on the subject.

**Diagnostic procedures:**

Hyperglycemia is the common feature of both Type 1 and type 2 diabetes. Besides, the symptoms of the two types are also identical and involve increased hunger (polyphagia), increased thirst (polydipsa), and copious urination (polyurea). This makes the correct diagnosis of the disease a bit tricky. The most important criterion for making a preliminary guess is the age of the patient. While

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type 1 diabetes sets in relatively early in life, type 2 diabetes is a late-onset condition. However, this information alone cannot be conclusive because the cases of type 1 diabetes have been reported in the elderly also. There are following methods to diagnose the hyperglycemia in subjects:

1. Measurement of HBA1C, which gives an idea of average blood glucose levels over a span of few months.
2. Measurement of fasting plasma glucose (FPG) which is ideally done after 8 hr of fasting.
3. Random plasma glucose test which measures plasma glucose
4. Oral glucose tolerance test: for this test the subjects are fed a sweet solution and readings are taken 2 hours before and after taking glucose. This test gives an idea of metabolism of glucose in the body.

**Genetic Basis:**

Diabetes, barring a miniscule proportion of cases, is clearly not a single gene defect. It is rarely caused by a single gene defect attributed to any particular gene such as hepatocyte nuclear factor-1A (HNF-1A) and glucokinase (Vaxillaire & Froguel P (2008). Instead, the disease may result from the defects in expression of all those genes which somehow play a role in glucose uptake by cells, hormone action, or carbohydrate and lipid metabolism. Such genes may be related to glucose transporters, receptors of hormones, molecules involved in signaling by insulin and other hormones, and also to key enzymes involved in metabolism of glucose. A study suggests that the risk of type 2 diabetes is 40% if one of the parents is diseased whereas the risk rises to 70% in cases where both the parents have type 2 diabetes (Tillil & Köbberling, 1987). There have been three main approaches for detecting the genes associated with type 2 diabetes – linkage analysis, probing candidate genes, and genome wide association studies (GWAS).

**(i) Linkage analysis:**

Genes involved in certain diseases can be identified by considering linkage of marker genes on certain chromosome loci associated with the genes of interest. This method is quite successful in detecting the genes linked with single gene defects but is not useful in detecting complex polygenic disorders such as type 2 diabetes. Of the genes that are implicated in type 2 diabetes on the basis of linkage studies is the CAPN10 gene which encodes for a cysteine protease belonging to calpain

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family and was the first gene discovered having a role in type 2 diabetes (Hanis et al., 1990). Even though this gene has been found to be associated with NIDDM in several studies (Song et al., 2004), yet this is not a consistent result (Zhou et al., 2010).

Another gene which is closely related to the risk of type 2 diabetes is the TCF7L2 (Transcription factor 7 like 2) gene located on chromosome 10q (Grant et al., 2006). Its protein product is a high mobility group box-containing transcription factor which possibly regulates proglucagon gene expression through Wnt signaling pathway. Haplotypes of TCF7L2 gene have been found to be associated with type 2 diabetes in various ethnic groups including the Mexican (Lehman et al., 2007) and Chinese populations (Chang et al., 2007).

**(ii) Candidate gene studies:**

Candidate genes are those genes whose function is known and which are somehow related to the disease. In the context of type 2 diabetes, all the genes related with glucose and lipid metabolism, glucose uptake and signaling mechanisms of hormones that regulate sugar metabolism can be considered as candidate genes. The study of such genes has been only moderately successful in identifying genes related to type 2 diabetes. Some of the key candidate genes identified in this manner comprise of ABCC8 (a sulfonylurea receptor), peroxisome proliferator-activated receptor gamma (*PPARG*), potassium inwardly-rectifying channel, subfamily J, member 11 (*KCNJ11*), insulin receptor substrate 1 & 2 (*IRS1&2*), Wolfram syndrome 1 (wolframin) (*WFS1*), HNF1 homeobox A (*HNF1A*), HNF1 homeobox B (*HNF1B*) and *HNF4A* (Ali, 2013). Polymorphisms of all the above mentioned genes have been shown to cause diabetes.

**(iii) Genome wide association studies (GWAS):**

This is by far the most successful method of identifying genes involved in development of type 2 diabetes. This approach focuses on single nucleotide polymorphisms (SNP) that are more frequent in type 2 diabetes. The technique of GWAS has identified several novel genes having a critical role in type 2 diabetes (McCarthy & Zeggini, 2009). The studies also give evidence of the role of obesity genes in diabetes which correlates with clinical findings. The GWAS data points to the key role of genes such as TCFL2 (described earlier), HHEX (hematopoietically expressed homeobox), SLC30A8 (solute carrier family 30 member 8), CDKNA/B (cyclin dependent kinase inhibitor

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A&B), IGF2BP2 (insulin like growth binding protein 2), *KCNQ11* (potassium voltage gated channel, KQT like subfamily, member 1) and *NOTCH2-ADAM30* (Notch 2-ADAM metallopeptidase domain 30). It is interesting to note that many of these genes relate more closely to insulin secretion rather than insulin sensitivity suggesting the critical role of β-cell function in the etiology of diabetes (Florez, 208).

**Epigenetic factors:**

Epigenetics involves alterations in gene function which do not change the sequence of genes (Weinhold, 2006). Recent developments have revealed the importance of mechanisms such as DNA methylation, histone deacetylation, and noncoding RNAs in regulating gene expression by varying chromatin condensation. These mechanisms are ubiquitous and form the basis of may diseases. They may also explain the impact of intrauterine influences on the foetus and their role in the development of conditions such as obesity and type 2 diabetes. The characteristics signatures in the epigenome from various tissues that may lead to obesity and type 2 diabetes have recently been reviewed (Ling & Rönn, 2019). Epigenetic mechanisms also explain the heritability of trends which have been observed over a short period of few generations which is too small a period to cause any alterations at the genetic level (Skinner, 2011).

**Environmental basis of the disease:**

It has become quite clear that the susceptibility and presentation of type 2 diabetes depends to a great extent on factors which fall outside the domain of genetics and relate to the life style and socioeconomic status of the subjects. Such factors comprise of dietary habits, mental stress, behavioural aspects such as sleep, and exposure to pollutants and toxicants. It is also influenced by traditional risk factors such as age, sex, adiposity, immunity and blood pressure (Talmud et al., 2010). Here we give a brief description of each of these factors in the light of suitable studies to support:

**(i) Dietary pattern:**

A number of recent studies indicate that diet has a strong influence on the development of type 2 diabetes. Some of the foods that have been found to accelerate the incidence of disease comprise of red meat (Pan et al., 2011), fast food (Hu et al., 2001), whole grains, and sweet beverages

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(Neuenschwander et al., 2019). However, fish meat was found to be beneficial in type 2 diabetes (van Woudenbergh et al., 2009). Similarly, food rich in vitamins A, D, K, and Mg were also useful in NIDDM (Mambiya et al., 2019).

**(ii) Lifestyle & Socioeconomics:**

There is no ambiguity in stating that type 2 diabetes is greatly dependent on socioeconomic status of individuals (Thomas et al., 2012). However, an interesting observation is that whereas the prevalence of type 2 diabetes was more in high income group people, the trend is reversing there. On the contrary, affluence is directly proportional to type 2 diabetes in developing countries. Besides, lifestyle has a key role in the incidence of this disease. Alcohol consumption, lack of sleep (insomnia), stress and other such behavioural features increase the risk of type 2 diabetes (Agborsangaya, 20o3).

**(iii) Drugs and Pollutants:**

The rise in the cases of type 2 diabetes coincides well with the growth of antibiotics market and also with the increase in production, usage and emission of pollutants. Organic pollutants such as pesticides have been demonstrated to increase the risk of type 2 diabetes, obesity and hyperlipidaemias (Lee et al., 2011). These chemicals also get bioaccumulated as they move up the food chain.

**Conclusion:**

The prevalence of type 2 diabetes is on the rise in global population. This is attributed to a number of factors – both genetic and environmental. Diabetes being a polygenic disease, the search for precise genes involved in its etiology becomes quite challenging. The difference of presentation between the two forms of diabetes calls for accurate diagnostic procedures and differential prognosis in both cases. Type 2 diabetes is of greater medical interest due to its considerably high prevalence than that of type 1 diabetes. This paper has presented a concise review of the important studies undertaken on the subject so far. Of particular interest are the epigenetic factors which are being unravelled rather recently. Such studies and reviews are quite helpful in choosing the right line of treatment against insulin resistance. An understanding of the mechanisms underlying type 2 diabetes will be crucial in developing more effective cures for insulin resistance.

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