

Enhanced Pro-inflammatory Response in Obese Individuals and the Association of TCF7L2 Gene Susceptibility in Type 2 Diabetes Mellitus

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Type 2 diabetes mellitus (T2DM) is a group of disease such as hyperglycemia, dyslipidemia and atherosclerosis. In T2DM cells are sluggish to respond to insulin and cause insulin resistance (IR). However, Obesity is the major risk factor for type 2 diabetes (T2DM) and Alzheimer's disease (AD) with associated metabolic disorders. In obese individuals having T2DM and/or AD the accumulation of lipid is increased in adipocytes results for increased regulation or the release of pro-inflammatory interleukins/cytokines and causes mutation in amyloid precursor protein and hampers impaired insulin activity. The WNT signaling pathway is involved in many physiological and pathophysiological activities. Wnt signaling plays an important role in the development of β -cell which is responsible for insulin secretion. If insulin is present in a very higher amount in our body that means insulin not utilized properly in body and caused type 2 diabetes mellitus (T2DM). To overcome this problem first we understand that how to WNT Pathway influences β -cell function and how to control them. Wnt binds to the Frizzled receptor, which prevents β -catenin phosphorylation and degradation. The β -catenin signaling pathway plays an important role in glucose homeostasis. Transcription Factor 7 Like 2 gene (TCF7L2) is expressed in adipose tissue & involved in WNT dependent regulation of adipogenesis. Genetic variants of this gene are associated with an increased strong risk factor for T2DM. The mechanisms are reduced insulin secretion is uncertain. TCF7L2 is a transcription factor involved in the WNT signaling pathway and is ubiquitously expressed. The expression of IL-1, IL-6, TNF- α , TGF- β cytokines gene was highly increased in T2DM cases while the expression of anti-inflammatory gene viz. IL-1Ra, IL-4, IL-10 and IL-13 were reduced in T2DM cases is well known fact. An effort has been made in to clarify the role of inflammatory markers in the development of T2DM associated metabolic disorders. Large number of studies are going on in order to understand the cause of this disease, both environmental as well as genetic factors have been found to be involved. The macrophage culture from adipocytes isolated from subcutaneous layer having high protein content which change the gene expression IL-1 β (Interleukin 1-Beta) simultaneously with high diet fed mouse model (HDFM) is used to understand this mechanism which showed increased expression of Amyloid Precursor Protein (APP) with high rate of inflammatory changes which results in deposition of (APP) in the brain. In results it showed that HDFM have enhanced APP expression and its microglia releases high amount of TNF- α (Tumour Necrosis Factor -alpha). It was also confirmed from the published reports that TCF7L2 SNPs are associated with reduced insulin secretion. The molecular mechanisms responsible for the reduced β -cell response as a function of the TCF7L2 genotype have not been defined. TCF7L2 is a WNT signaling-associated transcription factor that plays an important role in insulin stimulation production by β -cells. The studies concluded that obesity is a state of inflammation and with increase in obesity there is infiltration of macrophages and its associated immune cells, which causes various impairments in body results in T2DM and AD. The blocking IL-1 β or controlling increased inflammation or high APP expression in body may prevent the cause of various metabolic disorders especially T2DM.

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