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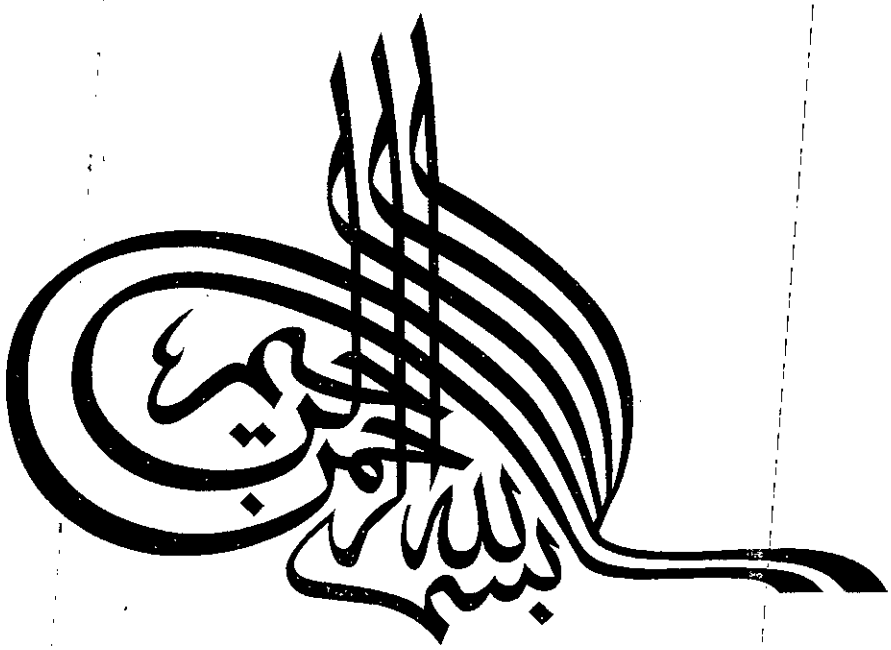
بسم الله الرحمن الرحيم

Study of the relation between the serum insulin level and peripheral vascular state in NIDDM patients .

THESIS

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Introduction

Non - Insulin - Dependent diabetes mellitus (NIDDM) accounts for over 85% of diabetes world wide [1] and is associated with an enormous amount of morbidity and mortality resulting from its microvascular , macrovascular , and neuropathic complications .

NIDDM is characterized by both fasting and postprandial hyperglycemia . In the fasting state , plasma glucose concentrations are maintained by a balance between hepatic glucose production (HGP) and glucose uptake by peripheral tissues [2-3] . Hormonal regulation of HGP is provided primarily by the combined effects of insulin and glucagon secretion , whereas glucose disposal is regulated by insulin and various other insulin - independent mechanisms .

In insulin resistance , the abnormalities in glucose disposal in NIDDM can be fully understod only by maintaining the same glucose concentration in diabetic and control subjects so that the mass-action effect of glucose on uptake is normalized . This is best accomplished with the euglycemic insulin clamp , which holds glucose level at 100 mg/dl and plasma insulin concentration at about 100 μU/ml . In patients with NIDDM ,

glucose disposal by muscle is then found to be about 60% of normal [4] . Thus , the most obvious site of insulin resistance in NIDDM is in muscle ; the liver defect is more complicated [5-6] . The liver was thought to be more sensitive than muscle to the effects of insulin [7] .

It now appears that the dose-response curves for insulin effects on uptake of glucose by muscle and HGP in NIDDM show comparable degrees of insulin resistance [8] .

The major uptake mechanism for glucose in muscle is the insulin-Sensitive glucose transporter GLUT-4[9-10] . Once inside the cell , most of glucose is stored as glycogen , or oxidized to carbon dioxide and water by pyruvate dehydrogenase in the krebs cycle ; very little is converted to lactate or lipid [11] .

The oxidative pathway of glucose is rate - limiting , but the insulin responsiveness of pyruvate dehydrogenase has been found to be impaired in NIDDM [12] .

Insulin secretion in NIDDM :

The function of the pancreatic β-cells in NIDDM has been studied intensively since the development of the insulin radioimmunoassay by Yalow and Berson in 1959 .

Their first studies produced the startling results that the plasma insulin concentrations in subjects with typical NIDDM were higher or equal to those in nondiabetic controls [13] .

This finding led to the conclusion that NIDDM is caused not by insulin deficiency but by an inability of insulin to lower plasma glucose levels effectively - an abnormality termed insulin resistance . The situation has turned out to be far more complicated than initially thought , because it is now clear that NIDDM is characterized by insulin resistance and a great number of abnormalities of islet-cell function .

More studies were done by karam and co-workers [14] who found that obese individuals have hyperinsulinemia , which compensates for their insulin resistance . Studies by Perley and kipnis then demonstrated that normal-weight subjects with diabetes secreted less insulin than did weight - matched normoglycemic controls and that obese subjects with diabetes secreted less insulin than did obese controls [15-16] .

In a normoglycemic population , fasting plasma insulin levels are quite variable and are a much better indicator of the severity of insulin resistance than of the functional capacity of β-cells . Thus , a low fasting plasma insulin level does not in any way indicate B- cell inadequacy , but instead reflects insulin sensitivity . In contrast , a high insulin level indicates the presence of insulin resistance , except for the rare patient with hyperproinsulinemia or a mutation of the insulin molecule for whom the immunoreactivity of circulating insulin is not accompanied by suitable biologic activity . In hyperglycemic states , the insulin concentration may be high with the level depending on the extent of insulin resistance , but no matter how high these concentrations are , the B-cells do not compensate sufficiently .

During a typical 24-hour day , plasma glucose concentration in persons with NIDDM remains elevated through - out , with excessive glycemic elevation after each meal .
In the state of mild to moderately severe NIDDM , the plasma insulin concentrations look similar to those for weight - matched controls [17-18] .