EFFECT OF PHYSICAL EXERCISE ON GLUCAGON AND GLUCOSE IN NON-INSULIN-DEPENDENT DIABETICS

THESIS

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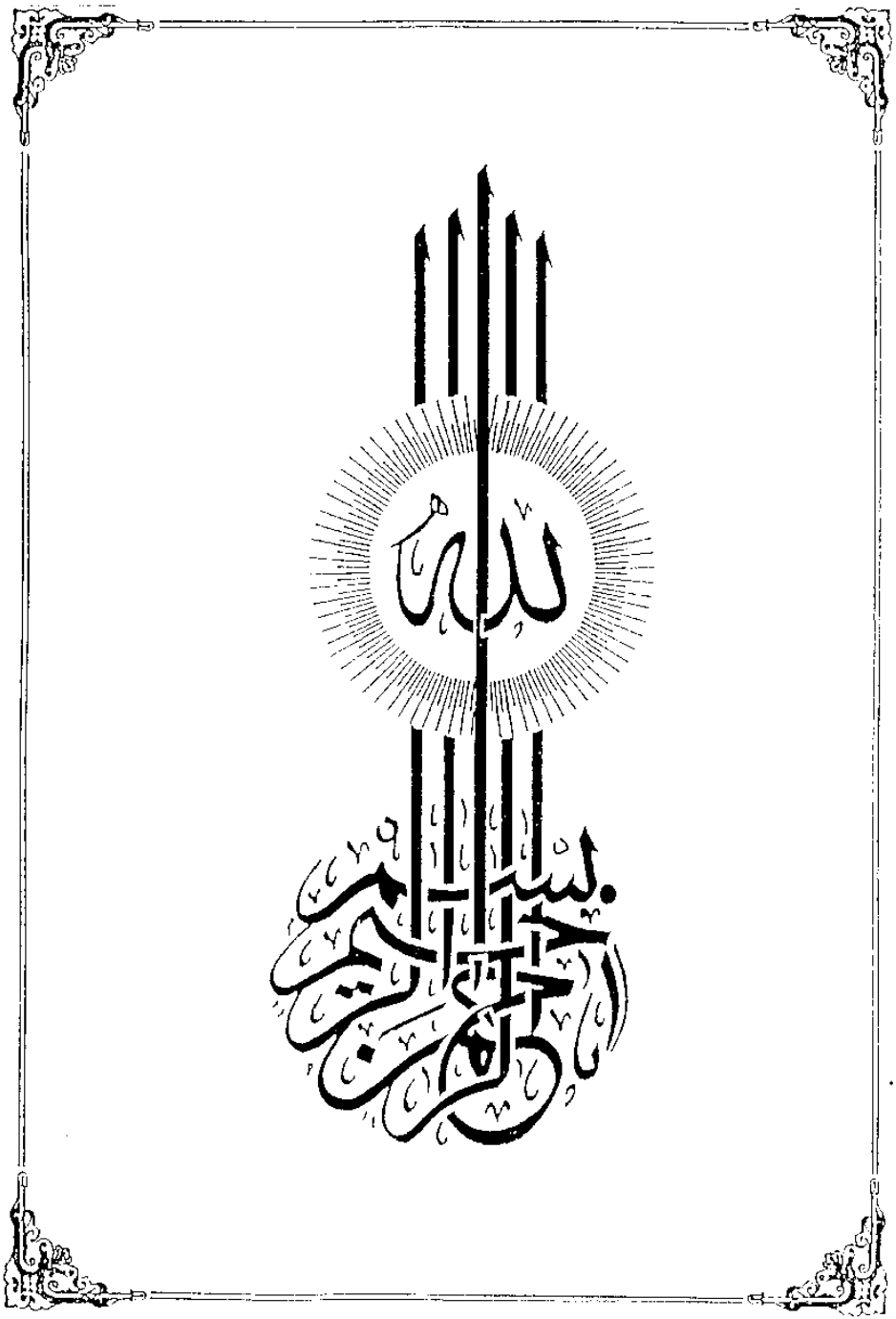
بسم الله الرحمن الرحيم

" وما توفيقي إلا بالله عليه توكلت
وإليه أنيب "

صدق الله العظيم

[سورة هود : الآيه ٨٨]



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In normal man, exercise causes little or no change in plasma glucose level *[Wahren, 1979]*. Nevertheless, exercise-related hypoglycemia is a major clinical problem in type I diabetics. In contrast, relatively little is known about the effects of exercise in type II diabetes. *[Schneider et al., 1987]*.

Deficient glucagon responses to decrements in plasma glucose, which are common in patients with IDDM and occur in some patients with NIDDM, result in altered counterrgulation *[Cryer and Gerich, 1985]*.

Wolfe et al., [1986] reported that during light exercise, there must be a reduction in insulin secretion and/or an increase in glucagon concentration if plasma glucose homeostasis is to be maintained. If such changes do not occur, hypoglycemia, and hence exhausion, may occur.

Glucagon plays a major role in stimulating hepatic glucose production, increasing both glycogenolysis and gluconeogenesis *[Kemmer and Vranic, 1981]*. In dogs, glucagon may account for as much as 70% of hepatic glucose output but in humans, however, glucagon deficiency does not

significantly impair the early glycogenolytic response to exercise *(Horton, 1988)*.

The aim of this work is to study the acute effect of physical exercise on plasma glucagon and blood glucose levels in noninsulin-dependant diabetic patients in order to evaluate the possible role of glucagon in pathogenesis of type II diabetes and as a glucose counterregulatory hormone during exercise.

REVIEW OF LITERATURE.

DIABETES MELLITUS

Definition :

Diabetes mellitus is a heterogenous primary disorder of carbohydrate metabolism with multiple etiologic factors that generally involve absolute or relative insulin deficiency or insulin resistance or both . All causes of diabetes ultimately lead to hyperglycemia, which is the hallmark of this disease syndrome. *(Olefsky, 1988).*

Diagnosis :

National Diabetes Data Group, 1979, considered any of the following criteria diagnostic of diabetes:

A)presence of the classic symptoms of diabetes, such as polyuria, polydipsia, ketonuria, and rapid weight loss, together with gross and unequivocal elevation of plasma glucose.

B) Elevated fasting glucose concentration on more than one occasion, venous plasma glucose ≥ 140 mg/dl [7.8 mmol/L].

C) Fasting glucose concentration less than that which is diagnostic of diabetes (B), but sustained elevation of glucose concentration during the oral glucose tolerance test on more than occasion. Both the two-hour sample

and some other sample taken between the administration of the oral 75mg glucose dose and the two-hour sample must meet the following criterion, venous plasma glucose ≥ 200mg/dl .

The National Diabetes Data Group, 1979, suggested the diagnosis of impaired glucose tolerance, if the fasting plasma glucose level is less than 140mg/dl and if the 2-h plasma glucose concentration is between 140 and 200 mg/dl and other value in the 2-h test peroid is equal to or greater than 200mg/dl .

Classification :

The 1980 report of the world Health Organization WHO, classified diabetes into :

1. Insulin-dependant, [IDDM] or type I. Formerly called juvenile-onset or ketosis-prone diabetes .
2. Non-insulin-dependant, [NIDDM], or type II formerly called adult-onset, maturity onset, or nonKetotic diabetes.
   A) Obese [about 80%]
   B) Nonobese [about 20%]
3. Impaired glucose tolerance [IGT]. Formerly called chemical, border-line, or subclinical diabetes.

4. Secondary diabetes

A) Pancreatic disease [e.g., pancreatectomy, pancreatic insufficiency, hemochromatosis].

B) Hormonal [excess counterinsulin hormones, e.g., cushing's syndrome, acromegally, pheochromocytoma] .

C) Drug-induced [e.g., thiazide diuretics, steroids, phenytoin].

D) Associated with specific genetic syndromes [e.g., lipodeystrophy, myotonic dystrophy, ataxia-telangiectasia].

5. Gestational diabetes : glucose intolerance with onset during pregnancy.

NON-INSULIN-DEPENDANT DIABETES (NIDDM) OR TYPE II

Definition :

Type II diabetes is defined in essentially negative terms : It is a nonketotic form of diabetes that is not linked to HLA markers on the sixth chromosome, it has no islet cell antibodies, and it is not dependent on exogenous insulin therapy to sustain life, thereby being termed non-insulin-dependant diabetes mellitus [NIDDM] *[Karam, 1988]*.

Aetiology and pathogenesis :

In Type II diabetes, plasma insulin levels are normal to high in absolute terms, although they are probably lower than predicted for the level of plasma glucose i.e., relative insulin deficiency is present *[Foster, 1980]*.

Obesity is a well known condition that leads to the development of insulin resistance; because the great majority of adult patients with type II diabetes are overweight, obesity-induced insulin resistance is frequently contributing factor in the hyperglycemia of these patients. *[Olefsky and Kolterman, 1981]*.

However, obesity cannot account for all of the insulin resistance in this type of diabetic patient, since many nonobese noninsulin-dependant diabetic patients are also insulin resistant. *[Reaven et al., 1976]*.

Significant decreases in numbers of insulin receptors have been demonstrated in a variety of tissues form obese human subjects *[Archer et al., 1975]*.

Postreceptos events or events that occur after insulin binds to the receptors, are currently thought to be responsible for insulin resistance *[Berger et al., 1985]*.

Diminished receptor number is considered an unlikely cause of NIDDM because of the abundance of extra receptors on the cell surface of insulin-sensitive tissue *[Cahill et al., 1987]*.

The binding of ^{125}I-insulin to monocytes is increased after acute exercise in untrained individual by increased receptor affinity and after a period of physical training by increased receptor number. *[Koivisto et al., 1979]*.

Relative hyperglucagonaemia is present in all forms of diabetes in which glucose production exceeds glucose diaposal and this causes endogenous hyperglycemia . In type II, the cause of relative hyperglucagonemia is unclear and

factors other than or in addition to insulin deficiency may be involved *[Unger and Orci, 1981]*.

Although the location of the genetic component for NIDDM is not known, possible changes have been noted on the eleventh chromosome, which contains the insulin gene but no HLA association have been identified in NIDDM *[Olfesky, 1988]*.

Clinical presentation :

Patients with NIDDM typically present with polyuria and polydipsia of several weeks to months duration. Polyphagia can occur but less common, whereas weight loss, weakness, and faitgue are frequent. Dizziness, headaches, and blurry vision are common accompanying compliants. *[Olefskey, 1988]*.

The hyperglycemia may lead to an increase in soft-tissue infections. In the female, fungal infection of the vulva are common, resulting in an abnormal discharge *[Cahill et al., 1987]*.

One quater to one third of patients have a family history of diabetes *[Cahill et al., 1987]*.

In many patients no symptoms are apparant and the disease is diagnosed by routine blood or urine testing. In