

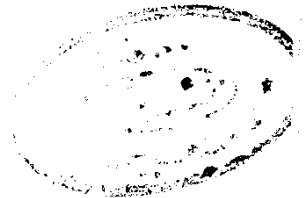
STUDY OF GLUCOSE UTILIZATION IN INSULIN DEPENDENT DIABETES (IDDM)

THESIS
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BY

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LIST OF ABBREVIATIONS

FAD	FLAVIN ADENINE DINUCLEOTIDE
HLA	HISTOCOMPATIBILITY ANTIBODIES
IDDM	INSULIN-DEPENDENT DIABETES MELLITUS
ICA	ISLET CELL ANTIGENS
LDH	LACTATE DEHYDROGENASE
NAD	NICOTINAMIDE ADENINE DINUCLEOTIDE
NADP	NICOTINAMIDE ADENINE DINUCLEOTIDE PHOSPHATE
PK	PYRUVATE KINASE

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Introduction & Aim of the work

INTRODUCTION AND AIM OF THE WORK

Type I diabetes is a syndrome characterized by a sudden clinical onset, severe hyperglycaemia and easy appearance of ketoacidosis, and severe insulin deficiency (Genuth, 1982).

Glycolysis "Embden-Meyrhopf pathway" is the oxidation of glycogen or glucose to pyruvate or lactate. Glycolysis is an important source of energy for the all cells. The glycolytic enzymes are sensitive to induction by insulin (Axelrod, 1967 and Harper et al., 1977).

So, it is important to study some of the enzymatic activity of glycolytic pathway in case of insulin dependent diabetes in order to clarify to what limit glucose oxidation via glycolysis is affected in type I diabetes.

Review of literature

INSULIN-DEPENDENT DIABETES MELLITUS (IDDM)**Definition:**

Insulin-dependent diabetes mellitus (IDDM) is a syndrome characterized by sudden clinical onset, severe hyperglycaemia and the easy appearance of ketoacidosis, and severe insulin deficiency (Gorsuch et al., 1981). It was reported that IDDM is the commonest endocrine disorder in childhood with frequent secondary complications (Porte and Halter, 1981). IDDM defines a group of patients who are usually, but not necessarily, under 30 years of age at the time of diagnosis. They generally present with an accelerating history of glucosuric symptoms for less than three months. They are thin and almost invariably exhibit weight loss. Only rarely are such patients discovered by testing for diabetes when they are asymptomatic; if so they may decompensate soon after (Fajans et al., 1976). This defines their state of absolute insulin dependency (Genuth, 1982).

Though a positive family history of diabetes, usually of a like type, may be obtained, only 10 per cent of such patients have either a diabetic parent

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or a diabetic sibling (Fajans et al., 1978). Functionally, IDDM is characterized by insulinopenia (Genuth, 1982).

Fasting plasma insulin levels are low, and there is little or no response to challenge with glucose, amino acids, tolbutamide, glucagon, or other beta cell stimulants. Anatomically, the islets are small and devoid of beta cells, though hyperplasia of other islet cells that produce glucagon, somatostatin and pancreatic polypeptide is often seen (Gepts et al., 1977). Ultimately, the beta cell function disappears as shown by low plasma levels of the connecting peptide molecule (C-peptide) which normally co-secreted with insulin (Malmquist et al., 1982).

A well defined subgroup of youthful-onset diabetics, sometimes known as MODY (maturity-onset diabetes of youth) or NIDDY (non-insulin-dependent diabetes of youth), may be diagnosed in their teens. Though these patients are usually treated with insulin, they are able to survive without it (Tattersall, 1974 and Fajans et al., 1978). In contrast, clinical onset in latter life by no means excludes a truly insulin dependent state.

CLASSIFICATION OF DIABETES MELLITUS

In the last few years different classifications of diabetes have been reported (Bottazzo & Doniach, 1976; Irvine, 1977). A major problem at present is that no classification is satisfactory for both the clinician and the researcher. In 1979, the National Diabetes Data Group (NDDG), developed together with the main Associations for the study of diabetes, a new classification of the disease.

The classification of diabetes mellitus and associated states proposed by the **National Diabetes Data Group, 1979** and provisionally endorsed by WHO (1980) is still the latest accepted classification (Keen and Tang Fui, 1982; Genuth, 1982).

CLASSIFICATION OF DIABETES MELLITUS (NATIONAL DIABETES DATA GROUP 1979, MODIFIED)

CLASS	FORMER TERMINOLOGY	AETIOLOGY
Insulin-dependent type (IDDM), type 1	Juvenile-onset diabetes ketosis-prone diabetes.	Genetic factors (increased frequency of HLA types), environmental or acquired factors, and abnormal immune responses seem to have an aetiological role.
Non-insulin-dependent (NIDDM), type 2	Maturity-onset diabetes ketosis-resistant diabetes	Heterogenous group with multiple aetiologies. Genetic factors seem to have an important role in the aetiology. Environmental factors superimposed on genetic susceptibility are probably involved. Obesity is suspected as an aetiological factor and is recommended as a criterion for dividing NIDDM into subclasses.
Other types, including diabetes mellitus associated with certain conditions and syndromes.	Secondary diabetes	In some of these types of diabetes, the aetiological relationship is known, in others, an aetiological relationship is suspected because of a higher frequency of association of diabetes with a syndrome or condition.

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This classification divides primary diabetes according to insulin-dependence. Nevertheless the sole criterion of insulin-dependence may be misleading because there are many non-insulin-dependent subjects that are treated with insulin for various reasons. Furthermore, among the non-insulin-dependent diabetic patients there is a small group that within a few months or years of diagnosis develop a clear insulin-dependence. To overcome these and other limits the same group proposed a parallel classification for research purposes (WHO Expert Committee, 1980).

The detection of islet cell antibodies (ICA), the association with organ specific autoimmune disorders, HLA typing and mode of inheritance are the main criteria of this subclassification (National Diabetes Data Group, 1979).

It has also reported that IDDM is subdivided into two groups: type Ia and type Ib (WHO Expert Committee, 1980). Type Ia has predominantly young onset, slight male preponderance, has a primary association with both HLA - DR₃ and DR₄ (Cudworth and Wolf, 1982).

In this subtype, identical twins may not be concordant for the disease, suggesting a genetic vulnerability to an environmental agent. Other autoimmune disturbances are not seen with increased frequency.

These patients are reported to produce somewhat higher titres of antibody to the exogenous insulin that is administered therapeutically (Genuth, 1982).

Type Ib- has predominantly middle-age onset which is oftenly insidious, striking female preponderance (Cudworth and Wolf, 1982). This type is characterized by having a strong association with HLA-DR₃. In this group, identical twins show a high degree of concordance for diabetes, suggesting a genetically conferred inevitability of the disease. Antibodies to islet cell antigens (ICA), which are transiently present in 80 to 90 percent of all patients with IDDM at the time of diagnosis, are more likely to persist in the serum of these patients (Genuth, 1982).

PROVISIONAL RESEARCH SUBCLASSIFICATION OF IDDM
(NATIONAL DIABETES DATA GROUP, 1979 MODIFIED)

Diabetes Mellitus			
	Association with organ specific autoimmune disease or autoimmune phenomena.	Presence of islet cell antibodies (in relation to onset of insulin dependency).	Other characteristics that offer promise of being used to subclassify diabetes.
Insulin-dependent type (IDDM)			
Subclass a	Positive	Usually persistent	Possible viral aetiology
Subclass b	Negative	Usually transient	prevalence of HLA types
Subclass c	Negative	Undetected	(elevated or reduced relative to the general population), such as DR ₂ , DR ₃ , B ₈ , etc.....; antibody response to exogenous insulin.

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