THE EFFECTS OF DIETARY GUAR GUM AND CELLULOSE IN THE DIABETIC RAT

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We, the undersigned, certify that

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ABSTRACT

The metabolic effects of two dietary fibers, guar gum and cellulose, were investigated in insulin-treated, alloxan-diabetic rats.

The diabetic rats fed a basal purified diet diluted with various levels of guar gum tended to have lower serum glucose concentrations ($P>0.05$) than the rats fed the basal diet diluted with the same levels of cellulose. An equivalent state of diabetic control (as evidenced by the similar serum cholesterol and triglyceride concentrations, the liver enzyme activities and the growth rates of the diabetic and the nondiabetic rats) was attained in all dietary treatments. However, the exogenous insulin requirements of the diabetic rats fed the guar gum diets were lower ($P\leq 0.01$) than the requirements of the rats fed the cellulose diets. The difference remained significant ($P\leq 0.05$) after adjustment of the insulin requirements with body weights.

Serum lipid levels were similar in both the diabetic and nondiabetic rats. A positive correlation was found between the serum glucose levels and the 5-hour fasted serum triglyceride concentrations ($r^2=0.05$). No linear relationship was found between the serum glucose and the serum cholesterol levels ($r^2=0.002$).

The growth of the rats decreased as the level of fiber dilution of the diet increased; the reduction in growth was

greater in the rats fed the guar, as compared to the cellulose diets ($P \leqslant 0.01$). Although the dry matter digestibilities of the guar diets were higher than the cellulose diets, the adjustment of the weight gains of the rats with the energy consumed resulted in no differences remaining between treatments. The smaller feed intakes, and hence weight gains, of the rats fed the guar as compared to the cellulose diets, were concluded to be due to the different physical properties of the two fibers. The satiety of the rats fed the guar diluted diets may have been increased by the greater viscosity of the digesta, or, alternatively, gastrointestinal discomfort may have been caused by the distension of the gut.

In conclusion, guar gum, but not cellulose, was effective in reducing the serum glucose levels and the exogenous insulin requirements of the alloxan diabetic rat. The difference in action of the two fibers could not be accounted for by differences in the feed intake patterns, the hepatic enzyme activities, the gastrointestinal transit times or the dry matter digestibilities of the diets.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. INTRODUCTION

Insulin-dependent, type 1, diabetes mellitus afflicts approximately 1.3 per 1000 children in the United States (Sperling 1979). The life expectancy of these diabetic children is two-thirds that of the normal child (Farquhar 1979). Almost all the excess morbidity and mortality in diabetics results from the development of chronic vascular disease, rather than from the acute lack of metabolic control (Bondy and Felig 1971). Microangiopathy is the predominant form of vascular disease occurring in the insulin-dependent diabetic (Hadden and Weaver 1979).

A relationship may exist between the development of microvascular complications and the control of the blood glucose concentration. Most prospective studies, and experimental data, support the contention that the hyperglycemia and, to a lesser extent, the insulin deficiency initiate and expediate diabetic microangiopathy (Cahill 1978, Tchobroutsky 1978). The majority of patients with insulin-dependent diabetes have poor blood glucose control and, frequently, elevated blood lipid levels, despite therapeutic treatment (Chase 1979). Diet therapy is an essential part of the overall management of diabetes. The dietary intake of an individual is balanced by a suitable insulin regimen. However, all insulins are absorbed slowly from the subcutaneous injection site and as a consequence, the peak in insulin activity

is difficult to correlate to the ingestion, digestion and absorption of food. Thus even those patients who are considered to be in good metabolic control have large diurnal fluctuations in blood glucose concentrations (Maurer 1979).

Various high carbohydrate, high fiber diets have been reported to increase the control of the diabetic condition (Anderson and Ward 1978). Although several aspects of the dietary composition are altered by the consumption of high carbohydrate, high fiber diets, Anderson and Ward (1978) suggested that the fiber component of the diet was the main cause of the changed metabolism. Supplementation of the diets of a small number of diabetics with guar gum, a mucilaginous dietary fiber, similarly resulted in an increased diabetic control (Jenkins et al. 1978b). The effects of long term supplementation of the diet with other fibers, on the diabetic metabolism, have not been investigated.

Rats injected with alloxan develop diabetes. These rats are characterized by a deficiency of insulin and the resultant metabolic condition has many similarities to the human insulin-dependent diabetic (Hoftiezer 1970). Preliminary investigations, into the effects of dietary components on the metabolism of diabetes, may thus be carried out using an alloxan-diabetic rat population.

The objectives of the present research were to examine the effects of addition of cellulose (the main dietary fiber component in high carbohyrate diets) and guar gum on various parameters of the diabetic condition in the insulin-treated diabetic rat. The growth and nutrient utilization of rats fed

the fiber diluted diets were also investigated.

2. REVIEW OF THE LITERATURE

2.1 INTRODUCTION

The term diabetes mellitus encompasses several different diseases (Jackson 1978) including the insulin-dependent, type 1, diabetes mellitus, which characteristically appears in childhood. At least two distinct forms of insulin-dependent diabetes mellitus (IDDM) exist; one of which is associated with the human leukocyte antigen (HLA) B8 and the other with HLA BW15. The first form of the disease is characterized by an increased prevalence of islet cell antibodies, a poor antibody response to exogenous insulin, an increased association with autoimmune diseases, and a higher incidence of microangiopathy. The second form of IDDM is characterized by a greater antibody response to exogenous insulin and is not associated with autoimmune disorders or islet cell antibodies (Redaksie 1978, Rotter and Rimoin 1978).

The prevalence of IDDM in the United States is approximately 1.3 per thousand children (Sperling 1979). Peaks in incidence occur at the ages of five to six and ten to twelve years, with an increased incidence in the winter months (Fleegler et al. 1979). Although morbidity and mortality as a direct result of diabetic hyperglycemia are small, the indirect consequences of metabolic abnormalities result in a high incidence of vascular disease. Careful control of blood glucose

concentrations has been suggested to inhibit or delay the long term development of diabetic complications (Tchobroutsky 1978).

2.2 ETIOLOGY OF INSULIN-DEPENDENT DIABETES MELLITUS

IDDM is caused by the failure of the beta cells, of the islets of Langerhans in the pancreas, to produce sufficient insulin for the needs of the body. The mechanism responsible for this failure is unknown. Susceptibility to diabetes is partially genetically determined, as 20% of all diabetics have a first degree relative with a diabetic history (Craighead 1978). The mode of inheritance, however, has not been elucidated.

Studies from different regions of the world have shown that a greater prevalence of IDDM is associated with various alleles (Nerup et al. 1979). However, despite these associations, studies of IDDM occurring in twins indicate that only 50% of monozygous twins are concordant for the disease (Sperling 1979)

Post-mortem studies have shown insulitis in 68% (Gepts 1965) and pancreatic islet cell antibodies in 85% (Rayfield and Seto 1978) of newly diagnosed diabetics. The peaks in diabetic incidence have been correlated with viral outbreaks in certain geographical areas (Craighead 1978) and a similar association has been reported between the seasonal pattern of diabetes development and the incidence of viral infections (Craighead 1978, Fleegler et al. 1979). Several viruses, such as coxsackie virus B_4, encephalomyocarditis virus and reovirus

type 3, have been shown to produce diabetes-like syndromes in mice (Yoon et al. 1979).

Rayfield and Seto (1978) concluded that both autoimmune processes and viral infections may be operable in the etiology of diabetes. The virus may act to trigger an autoimmune event, or an autoimmune phenomenon may act to increase susceptibility to a diabetogenic virus. Presently, both genetical and environmental factors are thus considered to be active in the etiology of IDDM.

2.3 SYMPTOMS OF INSULIN-DEPENDENT DIABETES MELLITUS

The clinical syndrome of IDDM varies greatly between individuals. The diabetic condition usually develops suddenly, often with no record of a previous illness. The untreated diabetic is usually lean, and the major symptoms of the disease are polydipsia and polyuria. Weight loss despite polyphagia, may also occur. If treatment with insulin and a controlled dietary pattern are not initiated, the patient will develop severe acidosis and eventually become comatose (Golovin 1978).

2.4 PHYSIOLOGICAL BASIS OF INSULIN-DEPENDENT DIABETES MELLITUS

2.4.1 Morphology of the pancreas

The pancreas of the insulin-dependent diabetic is often reduced in size and weight. LeCompte and Gepts (1977) suggested that this was due to the progressive atrophy of the tissue occurring in the diabetic state. In addition, the number and

size of the islets of Langerhans are generally reduced. The pancreas of the newly diagnosed diabetic contains both atrophic islets, which have only a few beta cells, and hyperactive islets. The proportion of atrophic to hyperactive islets varies within each region of the pancreas and in each diabetic (LeCompte and Gepts 1977). The evidence suggests that some islets are enlarged and hyperactive prior to the onset of clinical diabetes, possibly due to the increased circulating growth hormone levels. An injury of some sort then occurs which is directed specifically against the beta cells and which results in the formation of the atrophic islets (LeCompte and Gepts 1977).

As the duration of the disease increases, the beta cells gradually disappear from the islets of insulin-dependent diabetics, until, in the majority of patients, there are virtually no beta cells remaining (Gepts 1965, LeCompte and Gepts 1977). The islets are then composed of cells that produce glucagon, somatostatin and the human pancreatic polypeptide. The role of somatostatin and the pancreatic polypeptide in the pathology of IDDM requires further investigation (LeCompte and Gepts 1977).

2.4.2 Insulin and glucagon secretion

Insulin and glucagon, which are secreted by the beta and alpha cells of the islets of Langerhans respectively, exert opposing actions on glucose metabolism. The hormones act together to control the uptake and disposal of nutrients by the tissues of the body. Unger et al. (1971) studied the concentrations of insulin and glucagon, in the portal vein, in varying circumstances. An inverse relationship was found between the

molar ratio of insulin to glucagon and the need of the body for endogenous glucose production.

Release of insulin is primarily regulated by small fluctuations in blood glucose levels. Other nutrients capable of influencing insulin secretion are mannose and fructose (Matschinsky 1977), leucine and certain other amino acids (Floyd et al. 1970) and various lipid metabolites (Malaisse 1972). Insulin release is also influenced by the gastrointestinal hormones, secretin, pancreozymin and enteroglucagon (Malaisse 1972) and by the autonomic nervous system (Porte I976). Stimulation of the sympathetic nerves inhibits insulin secretion from the beta cells, while the activation of the parasympathetic nervous system causes an increase in insulin secretion.

Glucagon release from the islets is less well defined than that of insulin. Regulation occurs primarily by changes in the blood glucose and amino acid levels (Gerich et al. I974). High concentrations of glucose in the blood inhibit glucagon secretion, as does the presence of raised insulin levels. Amino acids, however, stimulate glucagon release (Porte 1976). Glucagon release is further regulated by epinephrine, pancreozymin, the autonomic nervous system (Porte 1976) and, possibly, by the free fatty acid concentration in the blood (Gerich et al. 1974).

The fasting concentration of plasma glucagon in the insulin-dependent diabetic patient is similar to that of the normal person (Unger et al. 1970, Sperling et al. 1977). However, hyperglucagonemia exists when the glucagon concentration is considered in relation to the prevailing blood glucose

levels. The amount of exogenous, injected insulin that reaches the alpha cells is significantly decreased compared to concentrations present in the islets after glucose induced insulin secretion (Lefebvre and Luyckx 1979). Unger (1978) suggested that an insulin concentration, excessive for the majority of the tissues, would therefore be needed by the islets to suppress glucagon secretion. Various reviewers have concluded that, although plasma glucagon levels are lowered by exogenous insulin, the normal relationship between glycemia and glucagon secretion cannot be restored (Raskin and Unger 1978, Unger 1978, Lefebvre and Luyckx 1979). However, both Matsuyama et al. (1975) and Sperling et al. (1977) have reported the alternate situation, and believe that insulin therapy restores the relative hyperglucagonemia to normal.

Although morphological studies of the pancreas indicate a substantial reduction in the number of beta cells during the course of the disease, some residual insulin secretion has been demonstrated in many insulin-dependent diabetic patients. Endogenous insulin secretion decreases with the increased duration of diabetes (Gjarwer et al. 1977). However, nearly 16% of patients studied (Ludvigsson and Heding 1976) had serum C-peptide levels within the normal range, even when the duration of the disease exceeded two years. The C-peptide concentration was therefore suggested to be unrepresentative of the biologically active insulin. Alternatively, Ludvigsson and Heding (1976) suggested that the level of endogenous insulin was ineffective due to a raised glucagon concentration.

The role of glucagon in diabetes mellitus has been

reviewed (Lefebvre and Luyckx 1979). Abnormal endogenous glucagon secretion was concluded to contribute to the development of hyperglycemia and ketosis in diabetes. However, metabolic abnormalities may also develop when undetectable levels of glucagon exist. Insulin deficiency is thus considered to be the main cause of the metabolic abnormalities in IDDM (Lefebvre and Luyckx 1979).

2.4.3 Action of other hormones in the body tissues

Various other hormones oppose the action of insulin in body tissues. Growth hormone is secreted by the anterior pituitary gland. In physiological concentrations, growth hormone opposes the action of insulin in a variety of tissues, including the muscle, liver and adipose tissue. The insulin antagonism caused by growth hormone, will usually be overcome by an increase in insulin secretion. However, if there is no increase in insulin secretion in response to an increase in growth hormone, hyperglycemia will result (Porte 1976).

Cortisol, which is released from the adrenal cortex under the influence of adrenocortical hormone, also acts to oppose insulin action in the liver and adipose tissue. Thus the activity of several hormones, such as glucagon, growth hormone and epinephrine, become evident. Epinephrine inhibits insulin secretion directly, by activating the pancreatic adrenergic alpha receptors. However, the epinephrine also activates the adrenergic beta receptors, which stimulate insulin secretion. Complete cessation of islet cell function, even during severe stress is, therefore, prevented. The main influence of

epinephrine on metabolism is its ability to inhibit the action of insulin in the muscle and to activate adenyl cyclase in liver and muscle, thereby promoting glycogen breakdown (Porte 1976).

The main hormones acting to create the metabolic abnormalities in IDDM are insulin and glucagon. The remainder of the neuroendocrine system acts to diminish, or accentuate, the effects of these two hormones.

2.4.4 Metabolic pathways in the uncontrolled diabetic state

The abnormal hormonal balance in diabetes results in a decrease in the activity of the major anabolic pathways of lipid synthesis, protein synthesis and glycogen synthesis, and an increase in the activity of the catabolic pathways of lipolysis, gluconeogenesis, proteinolysis, glycogenolysis and ketogenesis (Fritz 1972). The liver, muscle and adipose tissue are the primary sites of the metabolic abnormalities existing in the uncontrolled diabetic condition.

2.4.4.1 The liver

Glucose transport into the liver cells is an equilibrium process and is not modified by insulin (Newsholm and Start 1973). However, the rate at which glucose is utilized, or released into the blood, by the liver varies, depending on the concentration of several blood parameters (Bergman 1977). The direction and rate of the flow of carbohydrate through the metabolic pathways is regulated by the rate of the slowest reactions in the pathways. The rate limiting reactions

in glycolysis and gluconeogenesis are catalyzed by the unidirectional enzymes (Dunaway et al. 1978).

The activities of the three unidirectional enzymes of glycolysis, glucokinase, phosphofructokinase and pyruvate kinase, are decreased in diabetes. The reduction in activity primarily results, directly or indirectly, from a change in the insulin to glucagon ratio. Other metabolites, which inhibit the activity of one or more of the unidirectional enzymes, include the following: adenosine-3'5'-cyclic monophosphate (cAMP), adenosine triphosphate (ATP), citrate, alanine and 3-phosphoglycerate (Uyeda and Luby 1974, Niemeyer et al. 1975, Van Berkel et al. 1977). An increased concentration of glucose in the blood and an impaired ability of the liver to utilize this glucose results in the diabetic condition.

While glycolysis in the liver is reduced in diabetes, the production of glucose via gluconeogenesis is increased. The control mechanisms of gluconeogenesis in diabetes are not clearly defined (Exton 1972). Regulation of the rate of gluconeogenesis may occur at one or more of the reactions catalyzed by the unidirectional enzymes. The altered insulin to glucagon ratio in diabetes increases cAMP production via the activation of adenyl cyclase. However, although cAMP is known to play a major role in the physiological control of gluconeogenesis, the sites of action are uncertain (Exton 1972). Exton (1972) suggested that the major regulatory reaction of gluconeogenesis was probably that catalyzed by pyruvate carboxylase.

The overall rate of glucose production is influenced by other factors as well as by the activities of the gluconeogenic and glycolytic unidirectional enzymes (Exton 1972). The splanchic uptakes of alanine, lactate and pyruvate are increased by 50 to 100% in diabetes (Felig 1975). However, the plasma concentrations of the glucose precursors are either decreased (in the case of alanine and the other glycolytic amino acids) or normal (lactate and pyruvate)(Felig 1975). The increase in gluconeogenesis is thus due to an increase in the hepatic fractional extraction of the precursors under the influence of the decreased insulin, relative to glucagon, concentration (Exton 1972). The rate of glucose production via gluconeogenesis thus depends on the availability and the uptake of precursors as well as on the activity of the gluconeogenic enzymes (Wagle 1975).

The pathways of glycogen metabolism in the untreated diabetic are, similarly, activated to produce, rather than to store, glucose. The insulin to glucagon ratio, the plasma glucose and the glucocorticoid concentrations influence the activities of the enzymes of glycogen metabolism (Hers et al. 1970). A reduction in the amount of glycogen stored in the liver of the untreated diabetic results (Meissner and Legg 1971).

Increased lipolysis in the adipose tissue results in raised concentrations of free fatty acids in the plasma. The rate of beta oxidation increases but the oxidative capacity of the tricarboxylic acid cycle is limited and, when this has been exceeded, re-esterification of free fatty acids occurs.

Consequently an accumulation of fat in the liver results (Meissner and Legg 1971) and triglycerides are secreted into the blood as very low density lipoproteins. Alpha-glycerol phosphate, produced by the glycolytic pathway, is needed for the esterification of fatty acids. The production of alpha-glycerol phosphate is decreased in diabetes due to the reduced activity of the glycolytic pathway. The esterification of free fatty acids is, therefore, limited and the partial oxidation of free fatty acids to ketone bodies occurs.

Hepatic ketogenesis results not only from the increased concentration of free fatty acids in the blood, but also from the stimulation of the beta-oxidative pathway within the liver (Felig 1975). The major regulatory site in hepatic ketogenesis is probably the acetyl-carnitine transferase reaction (Lefebvre and Luyckx 1979). Ketone bodies are produced by the liver, in the untreated diabetic, in excess of the capacity of the peripheral tissues to utilize them. Ketosis therefore results, and ketone bodies are excreted in the urine.

The overall result of the metabolic derangements in the liver of the untreated diabetic is the underutilization, as well as the overproduction, of glucose. In addition, there is an increased metabolism of free fatty acids resulting in increases in the ketone body and triglyceride concentrations in the blood.

2.4.4.2 Skeletal muscle

The storage pathways in striated muscle are limited. Fatty acid synthesis does not occur and only a small amount of glycogen is formed and stored in the muscle (Meissner and Legg