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Analysis of Type II Diabetes Mellitus; the Metabolic Condition and its Proper Correction

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Abstract

Important features that characterize type II diabetes mellitus are described in relation to methods used to correct the condition. Unlike type I diabetes, type II is not proven to be an actual disease state since tissue abnormality has not been delineated with any certainty. Rather it is a metabolic condition that typically develops over a chronic time period of high caloric intake. When adipose tissue is filled with maximum triglyceride, assimilated foodstuffs are less efficiently stored even though insulin effects on the membrane of sensitive tissues remain functional. Diabetogenic substances were assayed for potency in causing beta cell damage and hyperglycemia. Their chemical structures were compared with agents used as oral type II diabetic drugs. Insulin dose response curves in stimulating glucose transport are analyzed. Although the use of diabetic oral agents in the treatment of type II are widespread, the reduction in glucose blood levels these agents achieve, to what would have been considered a normal range, is nevertheless abnormal. The proper treatment of type II involves caloric reduction to avoid prolonged hyperglycemia without use of oral drugs. Since elevated levels of insulin with largely intact functional effects characterize type II diabetes, it is not considered a disease but rather a state of over-nutrition.

Keywords: Diabetes; Insulin action; Isocaloric eating; Diabetic drugs

Introduction

One must consult with their physician before undergoing any significant change in the method by which diabetes is to be managed. Some people particularly the elderly have developed severe hypoglycemia after taking oral agents and then forgetting meals or fasting. This disclaimer is necessary to prevent such a phenomenon. In the case of type I diabetes, taking insulin and then forgetting to eat meals, or using insulin pumps improperly, had lethal consequences. Many concepts elaborated here remain controversial but require and deserve discussion.

Diabetes mellitus is a condition that is associated with glucose sugar being abnormally present in the urine as a result of high glucose levels in the bloodstream. The terms diabetes mellitus translated mean sweet siphon. When glucose levels in the blood

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become high enough so that glucose leaks through the kidneys into the urine, then not only is the urine sweet due to the sugar but also larger amounts of urine volume are excreted as well.

Although there are many causes of diabetes mellitus, two main types are recognized. Type I refers to those cases caused by a deficiency of islet cells in the pancreas that produce and secrete insulin. Type II refers to those cases that are associated with overeating since blood insulin is plentiful in spite of high glucose levels.

Although many argue this point in the Western United States, type II is completely correctable with dietary management without weight loss being necessary. Type I has been treated historically by nibbling small meals through the day as well, but the most used form of treatment today is the injection of purified insulin from animal or human origin to replace the blood insulin deficiency.

Experimental

Insulin function

The hormone insulin is secreted in response to meal eating. Blood glucose concentrations from 80 to 200 mg% cause progressive increased release of insulin from beta cells [1]. Then the blood insulin levels rise (from 0.2-0.9 ng/ml fasting to 5 ng/ml in the fed state) [2] and the hormone binds to muscle and fat tissue cell membranes to stimulate glucose uptake rates into these tissues several fold to promote storage of glucose as glycogen. Insulin also halts lipolysis for energy production and promote lipogenesis or lipid synthesis. In the liver, the hormone also blocks fat metabolism and promotes storage of glucose as glycogen and inhibits gluconeogenesis and release of glucose by the liver into the blood. At high doses to which the liver is exposed from the nearby pancreas, insulin also promotes synthesis of protein such as blood albumin. All together, these constitute the chief, well-understood reactions promoted by insulin that result in a lowering effect on blood sugar after eating a meal which typically elevates blood glucose to approximately 170 mg% [3] just under the renal threshold. Insulin dose response curves indicate that the hormone increases glucose transport rates in mammalian sensitive cells [4] and inhibits lipolysis [5] progressively over the range from 0.2 to 1 ng/ml at which point glucose uptake rates are maximal (FIG. 1) and lipolysis is a minimum. Miniscule increases above basal insulin substantially increase glucose transport rate quickly, but transport is maximal at fed state insulin levels so that concentrations above this produce no further increase. Insulin is the singular hormone that lowers blood glucose levels, while many hormones oppose this action of insulin.

Although insulin is degraded and can be taken up into cells, this is not a recognized component of its functional activity. Indeed, early studies by mentor, the late Dr. Arne N. Wick, demonstrated that labeled insulin after injection quickly distributes into a volume equal to the known volume of the systemic circulation (personal communication) that immediately, within minutes, quantitatively removes labeled glucose from the bloodstream [6] in mammals.

Some widely promote the notion that insulin increases the number of protein glucose transporters in the surface membrane of responsive tissues and that the hormone stimulates glucose uptake into cells over 10-fold faster than basal rates in the absence of insulin. However, all of our experimental data agrees with vast numbers of other insulin researchers indicating insulin increases the rate of glucose uptake by about 2 to 3 fold. In many of our experiments in which natural glucose is measured, uptake indeed is approximately doubled in a fixed time subsequent to insulin stimulation of fat cells. It is likely that in the living person or animal that insulin doubles the rate of glucose uptake and those observations higher than this were due to the

use of the nonphysiologic analog methyl glucose which is lipophilic. Moreover, our data indicate that the rapid stimulation caused by insulin occurs within a minute and can be compared to the increase in activity of a regulatable (allosteric) enzyme in a manner that supports the long held view first proposed by Dr. Pedro Cuatrecasas and later confirmed by Jeanrenaud and coworkers [7] as well as our studies [4,8] that the insulin receptor and glucose transporter exist in the surface membrane in a supramolecular complex that is directly stimulated by insulin binding to its surface receptor. Indeed, substantially increasing the fluidity of the membrane lipid bilayer even at levels that inhibits glucose transport rate does not affect the action of insulin in stimulating glucose transport.

The significance of these facts regarding the mechanism of action of insulin for the type II diabetic is that 1) it is unnecessary and indeed potentially harmful to ingest drugs designed to artificially elevate circulating concentrations of insulin above already physiologically-elevated fed-state levels, and 2) the coexistence of high blood sugar levels and high or normal insulin levels is not due to insulin insensitivity but rather is simply due to caloric overload. Caloric restriction attenuates hyperglycemia, and chronic isocaloric eating is the acceptable proper method of correcting the hyperglycemia of type II diabetes.

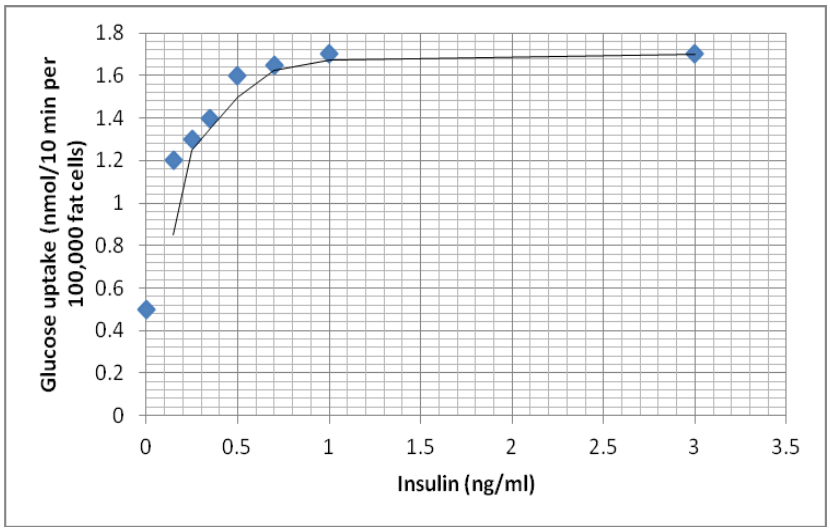

FIG. 1. **Cell glucose uptake as a function of insulin concentration. Data are from Hyslop, et.al. [4]. 200 pM=1 ng/ml=30 IU/ml. Similar curves are found in skeletal and heart muscle (data not shown). Insulin does not stimulate transport in liver which has glucose transporters freely permeable to glucose. Insulin exists at saturating fed state levels after eating a meal and normally returns to basal levels between meals, which then allows lipolysis and glycolysis rates to increase. 90 mg% (5 mm) glucose fully saturates glucose transporters in the cell membrane. Fed state glucose levels cause insulin to elevate to fed state levels and also saturate transporters that are stimulated by insulin.**

Type I Diabetes

In people who have damaged pancreas tissue that impairs insulin production and secretion, high levels of glucose in the blood are common with eating. A classic type I diabetic first notices symptoms of polyuria (high urine volume), polydipsia (thirst) and polyphagia (hunger) due to loss of sugar in the urine typically by the age of 15-16. These subjects without insulin can over the course of several days lapse into a type I diabetic coma because of the rapid metabolism of body fat for energy

since glucose cannot be utilized normally. Byproducts of rapid fat metabolism are acetoacetic acid and ketones that cause the blood pH (acidity) to drop to low enough levels approximately pH 7.2 from a normal value of 7.35 to cause loss of consciousness. Without treatment this situation may be lethal. Today serious diabetic coma may be quickly alleviated and prevented by injection of insulin.

Regular injection of insulin daily is the hallmark of treatment for type I, but because of its use a serious side effect is possible, known as an insulin reaction. This is caused by the injection of too much insulin or the injection of insulin in proper doses while forgetting to eat. In these cases too much insulin is present for the glucose level prevailing in the blood and the glucose level may be decreased to a point that is lethal (hypoglycemic coma). Insulin reactions have caused loss of life in insulin pump users due to continuous insulin infusion while mistakenly not eating, or in people who do not follow exacting instructions on insulin injection protocols.

Type II Diabetes

The classical or typical situation in type II diabetes is an individual who is an adult and is perhaps overweight and has eaten plentiful amounts of food for many years. Eventually such people (who have a very healthy pancreas and substantial levels of insulin) become unable to store excess food consumed as triglycerides in already enlarged fat cells and already filled glycogen storage granules in liver and muscle, and blood glucose can become elevated sufficiently to spill into the urine in spite of normal or elevated levels of insulin in the blood. This is not due to any intrinsic tissue disease or impaired insulin function [9], but is rather due to excessive caloric intake. Note that decreased activity levels with increasing age require caloric reduction to avoid inappropriate hyperglycemia. Calorie levels consumed regularly at an earlier age, that did not produce significantly high blood glucose levels, may nevertheless cause inappropriate hyperglycemia when the individual is more sedentary.

These individuals have classically been treated on the Eastern Coast of the U.S. by being admitted into a hospital ward immediately [2]. As stated, this is consistent with published data indicating that diagnosed type II diabetic patients with blood glucose levels as high as 250 mg% return to a normal glucose level of 100 mg% after a 15 hour fast. In the cafeteria setting, subjects are allowed access to 3 square meals daily with no snacking allowed. In all cases, the diabetes (urine sugar and inappropriate hyperglycemia) disappears within a few days and the subjects are allowed to return home. Patients learn that the condition they have is correctable by voluntary food restriction. Sometimes people are fearful enough of the possible deleterious effects of high blood glucose chronically that an immediate change in diet is followed where for example one might consume large amounts of vegetables in place of foods eaten before to cure themselves. However outpatient dietary success is usually reported as rare.

Partly due to pharmaceutical industry promotion, and partly to spare hospital bed space, in the Western United States a common practice is to administer diabetic oral agents on an outpatient basis to lower the patient's blood glucose artificially without requiring food restriction. These drugs bind to pancreas beta cell membranes and cause insulin to be released above the amount already secreted. This may be involved in causing in a few years in many people a compromised pancreas that does not secrete insulin normally [10]. This requires the patient to inject insulin from that point on. A more serious problem with the drugs is low blood sugar if meals are forgotten that would be similar to an insulin reaction in a type I diabetic. After

insulin treatment begins, the same fearful problems that plague type I diabetics are now possible in these subjects as well [11]. Many of the drug molecules employed have a structure similar to poisons used in high doses for research purposes to induce diabetes in experimental animals. Insulin levels are already normal or high in the untreated type II diabetic, which is why they are typically overweight, and artificially increasing insulin further with drugs merely produces additional abnormality. Earlier generation sulfonylurea drugs were banned in the 1960's by the FDA for side effects on the heart. Many of the drugs today are chemical derivatives of these, which evades the ban but without necessarily eliminating all side effects.

Many scientific papers argue that nonfunctional, abnormal insulin, or abnormal tissue resistance to insulin, or insulin receptor downloading may occur with the known high insulin levels typical in type II diabetes. However, people with type II typically have high body weight because their insulin is indeed functioning very well. All metabolic effects of insulin are known to be caused by the binding of insulin to high affinity receptors that alter receptor conformation that leads to the intracellular alterations. Insulin binding in the type II condition is sufficiently normal to cause weight gain, and glucose transport rates are fully stimulated by insulin at fed state insulin levels in adipose tissue cells as well. If intrinsic tissue abnormalities existed, independent of physical effects due to enlarged sizes of triglyceride-loaded fat cells, these individuals would tend to be thin or wasting as in type I diabetes, where a genuine insulin deficiency exists. Moreover, diabetic coma due to insulin deficiency that is seen in type I diabetes is not typical in type II.

Blood vessel degeneration

What happens in the type II diabetic who is not treated at all? Eventually high blood glucose levels that exist for perhaps ten years or so in an individual will typically cause blood vessels to become structurally altered and thickened. Initial symptoms experienced may be retinopathy (which over many more years may cause blindness), peripheral vessel alterations that could eventually lead to gangrene of the extremities, kidney vessel damage that can lead to kidney damage, and other vessel thickening that can lead to heart disease, etc. These symptoms are in common with symptoms in type I diabetes where hyperglycemia is due to insulin lack.

Results and Discussion

Insulin resistance reported experimentally with isolated obese large fat cells in floating suspensions, were subtle differences only at doses of insulin below blood levels actually present in the type II condition. It is thus of no known significance but unfortunately prompted the search for drugs to treat an 'intrinsic resistance defect' in type II diabetics whose blood chemistry is actually altered instead because of over-nutrition. Overeating causes high blood glucose even in the presence of fed state insulin levels that exist in obese type II diabetics. Note from FIG. 1 that insulin levels higher than 1 ng/ml do not stimulate glucose uptake beyond maximal since fed state insulin levels are saturate high affinity insulin receptors. Type II diabetes is associated with inappropriate hyperglycemia since both insulin and glucose remain chronically at fed state levels. To avoid such inappropriate hyperglycemia in type II diabetes, one must fast until glucose levels drop to the normal range before eating the next meal. Obese subjects typically chronically have insulin levels comparable to that in the fed state. This appears to be under genetic control. Although avoiding over-nutrition readily corrects inappropriate hyperglycemia, weight loss of course can be a more difficult challenge.

The motivation to eat properly in cases of type II diabetes, with the goal in mind of preventing long term blood vessel damage, is good. But it is not good to control blood sugar to the point that blood sugar meters are used throughout the day, and diabetic oral agents are taken to ensure sugar levels never exceed a particularly desired low level at any time to prevent any possibility of vessel damage in the future. Control obtained with insulin secreting drugs can cause more harm than good by stimulating the pancreatic islet membranes as when used as diabetogenic poisons to cause insulin to leak from the cells artificially [2]. In very low doses as prescribed to type II diabetics the patient does not become immediately a type I diabetic, and some patients tolerate the drugs quite well for long periods. But chronic use can eventually lead to a poisoned pancreas that is less able to secrete sufficient insulin in a subject who actually (before oral agent use) had a very healthy pancreas with plenty of secreted insulin. In fact, the high body weight individual with obesity has healthy blood levels of insulin where triglyceride and glycogen storage is very efficient. There is no better correlation in all of biology than the body weight of a person and the circulating blood level of insulin that is present on an average.

Diet

Type II diabetes or inappropriate hyperglycemia is basically a metabolic condition typically caused by consuming more calories than utilized daily for long periods of time. Diet treatment of type II diabetes has long been the hallmark of care and should remain so. Treatment centers on isocaloric eating, where the amount of calories consumed each day should balance the calories needed. In this way there is no overeating to the point where blood glucose becomes abnormally high or high enough to spill into the urine. There is no need to lose weight, as has commonly been argued, but simply one should eat in a non-weight-gaining mode. Experiments on animals with type II diabetes and in humans indicate that fasting completely corrects the high blood and urine sugar within 12-15 hours from the previous meal [12]. Isocaloric eating from that point on prevents recurrence of high blood sugar. Of course, the use of any oral diabetic drug must be discontinued before any reduction in calorie intake is begun. Oral agents taken without food can cause serious hypoglycemia akin to an insulin reaction in a type I diabetic.

Over the past many decades several excellent type I diabetic diets have been developed that are also applicable for patients diagnosed with the type II diabetic metabolic condition, such as the Mayo Clinic Diabetic Diet [13], the Bridges' Diabetic Diet [14] and the Diabetic Diet published by the U.S. FDA and the NIH [15]. All center on careful monitoring of total daily calories to match one's daily needs. No particular food needs to be eliminated from the diet as long as high calorie type foods (such as lard, butter, fat, etc.) are restricted to a given maximum so that total daily calories are not exceeded. Again, these diets are to be used only if one is not taking oral diabetic drugs. The first step is to eliminate the use of these harmful drugs completely. Then dietary management may be considered. One may join an organization such as Weightwatchers, not for the purpose of losing weight per se, but for help to eat the proper amount of calories each day to avoid weight gain (which is an isocaloric, diabetes correcting amount). In all classical cases of type II diabetes (blood sugar exceeding the renal threshold, or inappropriate prolonged hyperglycemia) will disappear.

On the Eastern U.S. seaboard, particularly at the Massachusetts General Hospital, oral diabetic drugs are not administered. On the West Coast, these drugs have gained wide acceptance. Understanding their metabolic effects, coupled with information on isocaloric eating to correct hyperglycemia, should help discourage further drug use.

Clinical experience

Countless patients over the years, dissatisfied with how their diagnosed type II diabetic condition was treated, achieved complete control of inappropriate hyperglycemia after learning to correct diet behavior. Often patients were found to be enamored with drinking soda pop. One subject consumed several liters daily, instead of eating traditional meals. With 39 grams of sucrose sugar in a 12 ounce can of soda, 1 liter bottles contain 124 grams of sugar. At two liters daily, 248 grams of sugar are consumed each day instead of water. Although the subject's physician prescribed oral diabetic agents to normalize blood glucose, the patients typically complained of feeling abnormal after taking the drug. Armed with information to stop drinking sugar-laden drinks after halting drug use, when outlaying the proposal to the physician, resistance was encountered with the statement that "you have an insulin resistance disease and you need to take the drug for the rest of your life." A second opinion was necessary, where the new physician allowed the patient the freedom to alter diet after stopping drug use on a trial basis, and the condition was completely corrected.

Patients can change dietary behavior when its significance is understood, and blood sugar levels return to normal without drugs. In other cases the dietary abnormality is not so obvious since many patients do not feel they "overeat" or agree to follow a diet plan, but may without realizing it be not actually in compliance, with extra eating almost subconsciously. Some individuals fear the consequences of long-term hyperglycemia in their diagnosed type II condition so that a totally vegetarian diet is chosen. This corrected their condition quickly in most cases, but it is not necessary. Humans have a pancreas with proteases and lipases for the purpose of digesting meat. However it is over eating any high calorie food that must not occur to correct type II.

Many people are diagnosed with either 'prediabetes' or type II diabetes that should not be. One case involved a subject with a fasting blood glucose level of only 101 mg%, who was prescribed an oral diabetic drug. This level, as stated previously, is in the normal range, and the order was likely due to pressure from drug company-provided brochures and salespersons arguing the case for drug use even at this level. In this case, no action was necessary. The definition of "prediabetes", the precise level of sugar in the blood after fasting that constitutes a need for concern, varies widely among groups. The American Diabetes Association states that any level below 130 mg% is considered within the normal range. So the goal should be to practice diet regulation until the blood glucose is routinely below this level prior to eating the next meal.

Another case was a subject diagnosed with type II and prescribed a drug who had a fasting glucose level of 125 mg%. The subject was told the drug is necessary to correct the "disease" that had appeared. This patient then followed a diet that did not contain free sugars, and the fasting glucose level has remained consistently at 90 mg% since then. Again, chronic, essentially permanent glucose levels above 130 mg% are a concern since elevated HbA1c over a sufficient time period may cause the protein glycation to become irreversible, and after 10 years microangiopathy could begin to produce symptoms. However such situations are usually due to chronic overeating as mentioned, that can be corrected, or in rare cases to some condition other than classical type II diabetes.

It is clearly possible that even a vegetarian diet, if it were overindulged with calorie-rich vegetables would not correct the hyperglycemia of type II. The caloric content of all types of vegetable, dairy, meat, condiments, breads, desserts, etc. have been measured and published in detail in McCance and Widdowson's, the Chemical Composition of Foods [16], now

available online. Overconsumption of such items as butter beans (283 calories per 4 ounces), peanuts (606), walnuts (551), almonds (600), honey (315), biscuits (485), desiccated coconut (630), dates (270), and other items would be problematic. In those cases where these foods are not overeaten, the hyperglycemia is easily corrected because the vegetables substitute for other foods that would have been consumed instead, such as bacon (526), lean ham (435), pork (330), steak (224), butter (793), cheeses (423 typical), egg yolk (350), margarine (704), chocolate cake (468), etc. Natural whole fruit sugars for sweetness in the diet are recommended over artificial sweeteners or high levels of refined sugar as in sodas. Many countries widely use acarbose, a natural polysaccharide that inhibits conversion of ingested carbohydrate to free glucose, with success in chronically lowering blood glucose levels [17]. Again, it is not necessary to eliminate any wholesome food from one's diet, but what is necessary in the face of the type II hyperglycemic metabolic condition is to refrain from excess calories and to eat a balanced diet with any particular food ingested in moderation.

Experimental diabetogenic agents and anti-diabetic drugs

Known poisonous substances have sometimes been used at lower doses to attempt to treat disease but this usually backfires, such as administering arsenic to treat syphilis or fluoride to treat osteoporosis. In the diabetes field, agents used experimentally to deplete beta cells of insulin, to study the effects of chronic hyperglycemia, led some to suggest use of these agents at lower levels in the treatment of type II diabetes since these subjects are replete with insulin. A wide variety of chemical derivatives of urea interact with protein sites on the surface membranes of cells. Treatment of organisms *in vivo* with urea derivatives that have a glucose-mimicing moiety or a hexacyclic organic structure typically cause covalent oxidation of sulfhydryl groups to disulfides in key proteins on beta cells of pancreatic islets [1]. These agents first cause alterations in stimulus secretion coupling of insulin (rather than other physiologic effects) because of the unique sulfhydryl-containing proteins on beta cell membranes that are responsible for insulin secretion in response to glucose challenge. For example, alloxan and streptozotocin irreversibly modify islet membranes causing artificial release of insulin. A single treatment with a sufficiently high dose causes or prolonged treatment at lower dose, cause depletion of insulin from storage granules and complete poisoning of beta cells, as far as insulin secretion is concerned [1]. It is also likely that long-term use at lower levels can cause a similar effect. Here glucose levels are first lowered by the abnormal insulin release and then elevated due to permanent insulin lack. In experimental laboratories around the world for the past many decades, streptozotocin and alloxan have been given in doses that permanently induce a type I insulin deficient diabetic state in animals for research purposes as originally discovered by Lazarow [18]. The molecules are thought to enter a glucose receptor and, due to the attached reactive urea, nearby sulfhydryls involved in insulin secretion are covalently altered.

In modern times, type II diabetes in the Western half of the U.S., in Denmark and throughout Europe is commonly treated with a variety of hexacyclic organic derivatives of urea in low doses [2]. It is thought that such treatment safely causes insulin release in a controlled manner, allowing type II diabetics freedom to live and eat calories without restraint while having no fear of hyperglycemic complications. However such medicines after years of use can stop lowering high blood glucose levels in these patients. The usual explanation is thought to be that the "diabetes worsens in the patient during the treatment program" and is thus no fault of the drug itself, or that the patient becomes harmlessly "resistant to the action of the drug" [19]. However, an alternative explanation is that these hexacyclic organic urea derivatives act comparable to alloxan and streptozotocin in experimental animals and eventually cause a state of permanent insulin deficiency in these subjects.

For a period of many years (1972-1976), we investigated the effects of steptozotocin on body weight, urine volume, glucose levels, and overall health of injected animals. Male Sprague Dawley rats were housed with ad libitum feeding and water in lots of 7 animals each. Experimental groups were injected introperitoneally with streptozotocin (55 mg/kg) in citrate pH 5 buffer. Age-matched control animals were injected with citrate buffer without drug. The animals were observed for appearance and behavior repeatedly each day over a several week period.

Control animals were unaffected by citrate buffer injection. They exhibited normal behavior, growth rate, body weight increases with time and normal urination. Rats injected with streptozotocin exhibited variable degrees of visible abnormality. Approximately 20% of the injected animals seemed to be essentially identical to normal controls in terms of appearance, weight gain, urination frequency and volume, and behavior. But the remaining animals exhibited severe polyuria, polydypsia, polyphagia, deficient weight gain, malaise, and lethargy. Cage bedding (sawdust) required changing daily due to excessive urine even though only 4 animals were housed together per cage. Control rats needed cage cleaning only every 5 days. Two water bottles per day were required for ad libitum drinking compared to 1 bottle of water every 3 days for normal rats. Of the animals exhibiting polyuria and deficient weight gain, about one fourth of those were extremely thin and became immobile, quickly became completely covered with urine and died 8-10 days after injection. The remaining streptozotocin injected rats lived for many weeks and did not revert to a more normal urination status at any time throughout the observation period.

It is well known that streptozotocin (2-D-glucosyl-1-methyl,1-nitrosourea) and alloxan (cyclic 4,5,6 carbonyl urea) are convenient agents for inducing a type I diabetic type state in rats, rabbits, mice, dogs and other animals for investigational purposes. The effects of injection of these drugs on young animals is sometimes reversible [1], but we did not observe this phenomenon in the present study. One possibility is that young rats post injections are still reproducing islet tissue that is completed at young adulthood [1]. 55 mg/kg doses are typically used by investigators to achieve a permanent hyperglycemic state with a single injection of streptozotocin. We find that such a treatment induces polyruia which is known to be due to hyperglycemia exceeding the renal threshold [1] with this dose in 80% of the treated animals [12]. Water intake is greatly increased and growth is impaired in these animals as well. Weight gain is completely obliterated in about 20% of the streptozotocin injected animals (1/4 of the diabetics) and is dramatically diminished in the other diabetic animals. Only 20% of streptozotocin injected rats seemed to be unaffected by the treatment. This is possibly due to missing the peritoneal cavity with the injection and has been observed and discussed in careful streptozotocin injection studies previously.

The published LD_{50} for streptozotocin is listed as 55 mg/kg for dogs and 137 mg/kg for rats. Our results indicate that the lethal effects of this agent are indeed due to its effects on insulin release that cause a lethal type I diabetic state About 25% of the animals did not survive the 55 mg/kg dose in our experiments, consistent with the reported LD_{50}. Other animal strains at various ages may exhibit somewhat different sensitivities, particularly since islet reproduction continues until adulthood in these animals, as in humans.

It is known that streptozotocin and alloxan treatment of adult animals causes multiphasic changes in blood glucose levels [1]. An initial phase of hypoglycemia is followed later by permanent hyperglycemia, polyuria, hyperglycuria, polydipsia and weight loss. The time dependence of these effects have been interpreted as being due to an initial interaction of the drug with the beta cell membrane causing artificial release of insulin from beta cell storage granules with hypoglycemia. This is followed

within 24-48 hours (at these high drug doses) by the diabetic state that correlates with the decreased blood level of insulin that occurs as a result of permanent insulin depletion by the agent. Alloxan works in a similar manner. High doses of these agents might cause severe hypoglycemia akin to an insulin reaction (prior to the observance of a permanent chronic diabetic state) but we did not examine this effect.

It was at one time thought that the functional portion of the alloxan molecule that is responsible for the effects were adjacent carbonyl groups [1]. But later it was deduced to be the carbonyl group in the urea portion of the hexacyclic organic molecule that is most efficient in inducing permanent diabetes in living organisms. An intact ring has been found also to be a requirement [1].

Oral antidiabetic drugs are also hexacyclic organic derivatives of urea, and probably exert their metabolic effects in type II diabetic patients in a manner similar to that observed for streptozotocin and alloxan when given in low doses. The effects caused by given doses of the most commonly employed agents for these purposes are known. Doses of alloxan and streptozotocin in the 1 uM range cause insulin release from pancreatic islets. This is within the range routinely employed for starting doses for diabetic drugs (from 0.25 uM to 92 uM). Furthermore, the LD_{50} for streptozotocin and alloxan have been determined by other investigators to be approximately 1-3 mM (depending on the animal species tested), comparable to the LD_{50} for the oral diabetic drug glypizide of 4.7-15 mm [20-22]. These data probably reflect the common effects on beta cells that are caused by the urea carbonyl moiety coupled with a hexacyclic organic ring that all these agents contain.

Diabetogenic agents such as alloxan administered at low doses comparable to those used in the treatment of type II diabetes indeed cause insulin leakage through the beta cell membrane as initially reported by Lazarow [1,18]. The well-known multiphasic levels of circulating blood glucose subsequent to injection of diabetogenic doses of streptozotocin or alloxan are explained by the initial period in which insulin release occurs, followed by permanent type I diabetes after insulin is depleted by the drug.

When the urea portion of streptozotocin is attached at other carbon positions on the ring, the substance is inactive in this regard. It is likely that urea needs to be positioned para to other substituents on the ring to enable the molecule to penetrate sufficiently into the membrane glucose receptor region involved in insulin stimulus secretion coupling. Note that many type II drugs have this para arrangement and that the organic ring is no larger than glucose in three dimensional space.

The relative water solubility of various parts of these molecules may influence their efficacy. Glipizide and glyburide are most potent at causing artificial release of insulin. Streptozotocin and alloxan are comparably effective, while a higher dose is required for tolazamide and chlorpropamide. Tolbutamide requires the highest starting dose. Urea itself (during human uremic poisoning) causes glucose intolerance, but its poisonous effects may be due to perturbations of proteins that are more physiologically critical. Urea is fully water soluble and would require extremely high doses to be insulinopenic, where other functional processes would already have been attenuated. The organic derivatives of urea here are more selective in affecting the glucose receptor region of the beta cell plasma membrane.

As stated previously [2], type II diabetes should not be treated with these agents. These include all urea and particularly sulfonylurea derivatives listed here that are sold and prescribed under such clinical names as diabeta or micronase (glyburide,

1-[[p-[2-(5-chloro-O-anisamido) ethyl] phenyl] sulfonyl]-3-cyclohexylurea), glucotrol (glipizide, 1-cyclohexyl-3-[[p-[2-(5-ethylpyrazinecarboxamido)ethyl] phenyl]sulfonyl]urea), diabinese (chlorpropamide, or 1-[(p-chlorophenyl)sulfonyl]-3-propyllurea) (220 mg/100 ml at pH 6), orinase (tolbutamide, or 1-butyl-3-(p-tolylsulfonyl)urea), and tolinase (tolazamide, 1-hexahydro-1H-azepin-1-yl)-3-(p-tolylsulfonyl)-urea). The sulfonyl group in diabetic drugs and the nitroso group in streptozotocin and the carbonyl in alloxan are adjacent to the urea carbonyl. Metformin (glucophage), a common antidiabetic agent that has found widespread longterm effective use, works by a different mechanism, by decreasing glucose output from the liver. Metformin and phenformin (now recalled from use) are dibiguanides (DBI) where DBI does not refer to the drug class, but instead was the experimental label of "diabetic dog 1" when the agent was first tested for antidiabetic properties in research animals (personal communication, Dr. Arne N. Wick).

Diet regulation is preferable to use of diabetic drugs

In an earlier study we recommended isocaloric eating or diet suppression techniques as the safest and most proper treatment for type II diabetes mellitus, inasmuch as obese mice and obese diabetic humans exhibit complete normalization of hyperglycemia from fasting after a previous meal [10]. This is consistent with the known fact that new cases of type II diabetes were non-existent during wartime rationing through both World War I and World War II [10]. Typical foods eaten per person PER WEEK during the food rationing of World War II were: 1 egg, 4 ounces of margarine, 4 ounces of bacon, 2 ounces cheese, 2 ounces jam, 2 ounces candy, one quart milk. Although this appears today to be a near starvation diet, the existence of type II diabetes was impossible with such rationing.

Newly diagnosed type II diabetic patients are admitted into the Massachusetts General Hospital's Joslin Diabetes Center hospital ward for purposes of teaching cafeteria meal-eating until blood glucose is normalized. This method has routinely been used to cure type II diabetes for many decades. Hospital admission was used to avoid non-compliance of dietary guidelines that typically occurred on an outpatient basis. Current methods of treating patients casually on an outpatient basis in other parts of the world with the above widely available oral drugs is not in keeping with safe and appropriate health care. Typically for many of the drugs, resistance can occur as well as the eventual conversion into a state where exogenous insulin is used in addition to the drugs.

The potential for severe hypoglycemia in patients taking medication who might forget to eat or who desire to fast can be dangerous, as of course are insulin reactions in type I insulin dependent diabetics. Thus, any attempts to wean subjects from such medication must be carefully planned by the patient's physician. Drug stoppage must precede fasting in such subjects of course. In many cases second opinions must be sought to obtain guidance with dietary methods that might have been discouraged or avoided by other practitioners who have been led to prefer drug use. It is important to emphasize that the older traditional method of treating obese type II diabetics with weight loss procedures is not necessary since normal glucose levels are achieved quickly following diet restriction followed by iso-caloric eating, as recently reviewed by Williams and Kelley [16]. Weight loss programs can often be difficult for many to attain.

Uncontrolled hyperglycemia (that is not treated with medication) is a more desirable alternative than having any permanently damaged islet cells from drug use. It requires about 10 years of improperly controlled hyperglycemia (no drugs and improper eating) on an average before microangiopathic alterations are detectable in type II diabetics. Moreover,

hyperglycemia is not ketosis-prone in type II diabetes because insulin levels remain normal or elevated and prevent lipolysis in these subjects (as long as oral agents have not deteriorated the beta cell membrane).

Unfortunately, patients are commonly switched from oral agents to insulin injection as a regular and now routine diabetic treatment program if the drugs lose full effectiveness, when the condition without drug treatment has not been reported to typically develop into a state of absolute insulin deficiency. The notion that diabetic drugs lose their effectiveness after a few years of use because of a natural deterioration of the type II diabetic state to an insulin requiring one is unlikely. Any effects of drug treatment may be permanent, in light of the finding that streptozotocin diabetes is irreversible after its one time experimental treatment in mammals. One possibility is that chronic low dose drug use eventually (by circulating 24 hours a day) modifies a certain fraction of sensitive proteins in the beta cell membrane involved in stimulus secretion coupling. Another possibility is that chronic use eventually depletes insulin significantly from storage granules inside beta cells. In any event, drug treatment itself is more harmful (quick artificial insulin stimulation and beta cell membrane alterations, etc.) than the long term chronic effects typically associated with the untreated hyperglycemia of type II diabetes. Insulin reactions caused by 1) drug ingestion coupled with forgetting to eat or with fasting or 2) administering insulin to a type II diabetic after drug treatment has run its course are potentially more serious than secondary effects of long-term untreated hyperglycemia. In any event, there is ample time to gain dietary control of prevailing sub-renal threshold hyperglycemia, often referred to as ‘prediabetes’, before microangiopathy ensues.

Use of insulin to correct the type II diabetic state, knowing that these subjects are normo or hyperinsulinemic, without measuring the patient’s circulating blood insulin level first, is improper. Such use at the very least causes weight gain and prevents the return to normal basal circulating insulin levels that should exist between meals. Low blood glucose for example halts beta cell insulin release at approximately 100 mg% in isolated perfused islets. Chronic elevated insulin associated with type II, with its prevailing chronic fed state insulin levels, and type II patients treated with exogenous insulin and insulin-secreting drugs, likely cause unnecessary tissue growth in the heart since insulin stimulates protein and triglyceride synthesis while blocking proteolysis and lipolysis. In type II diabetes, fed state insulin levels basically convert heart tissue into a glucose consuming tissue, rather than the normal condition alternating between fatty acid (between meals) and glucose (postprandial) use for energy. Oral drugs accentuate glucose use by the heart by increasing insulin levels. This increases collagen protein synthesis that may eventually cause the heart muscle myopathy known to be elevated in incidence in this condition. It is thus not surprising that cardiovascular heart disease incidence progressively decreases from type II patients treated with insulin or insulin plus oral insulin secretagogues, followed by treatment with drugs alone, followed by type II patients not treated with drugs or insulin [11]. Unfortunately, as of 2009, 84% of type II diabetics are treated with drugs, and 14% are treated with drugs plus exogenous insulin.

Blood chemistry in type II

As discussed previously, type II diabetes is a chemical condition caused by a perturbation of the normal dynamic equilibrium system that regulates blood glucose within normal limits. The normal maintenance of blood glucose levels within a controlled range is a dynamic equilibrium because glucose is continuously being assimilated while also continuously being metabolized and stored, or excreted while the blood glucose level remains relatively fixed. Normally when glucose blood levels are below the renal threshold, not being excreted in the urine, ingested glucose assimilated into the bloodstream

obviously equals the glucose amount that is either metabolized to pyruvate by systemic tissues, or during meal eating is stored as glycogen principally in muscle, liver, and fat. In this way, the concentration of glucose in the blood is regulated within the normal range, where typically fasting levels are from 81 to 108 mg% [3] (80-150 mg%) in elderly.

In type II diabetes, glucose levels in blood exceed the normal range largely due to increased caloric intake. Much like perturbing the equilibrium state of a chemical reaction, increasing the reactant (ingested glucose assimilated into the bloodstream) according to Le Chatelier's principle must cause a shift in the dynamic equilibrium to form more products. Since insulin levels are typically at maximum fed state levels in Type II, glucose transport stimulation at the membrane level and glucose storage as glycogen are maximal. When assimilated glucose amounts exceed this, blood glucose concentrations rise. If the blood concentration were to exceed the renal threshold of typically 230 mg/% (not typical in Type II), glucose spills into the urine and is excreted. An equation may be written that describes this situation as:

$$G_{ing} \rightarrow G_{metab} + G_{eliminated}$$

Where G_{ing} is the amount of glucose that is assimilated into the bloodstream after ingestion, and the product terms represent the amounts that are metabolized for energy or storage, plus that excreted. Increasing the reactant level on the left with excess caloric intake causes elevations in products formed, including glucose metabolized and glycogen formed plus in extreme cases glucose excretion into urine.

Much like a reaction in static equilibrium where the rate forward equals the reverse rate, it is useful to consider the dynamic equilibrium governing the process in the bloodstream. As long as the glucose intake equals the glucose removed from the blood through metabolism, the blood glucose concentrations remain normal, with levels between 90-130 mg% prior to the next meal. When glucose intake exceeds a normal amount needed to maintain metabolism and storage, then blood glucose will exceed the normal range. In other words, high caloric diets can cause elevated storage of glycogen and fat until there is no ability to store more. At this stage, the continued high rate of ingested glucose will not be able to be removed from the blood as rapidly as it is assimilated, and then eliminated glucose in the urine becomes significant. The rate of glucose metabolism and storage during fasting is determined by the rate at which glucose transport proteins uptake glucose through surface membranes of tissue cells. During meal eating, Beta cell release of insulin causes increased glucose transport rates so that the rate of metabolism and storage increases to accommodate the increased amount of glucose assimilated. Insulin levels are elevated while fed state glucose levels are high, and progressively return to basal levels as glucose levels subside to fasting concentrations. Normally during meal eating, the ingested glucose increase causes metabolized glucose to increase, and with help from increased insulin release, the level of blood glucose is maintained within a normal range, far below the renal threshold. In type II diabetes, fed state levels of insulin predominate continuously along with unnecessarily high increased caloric intake. Blood glucose levels do not return to normal basal concentrations when storage of glucose as glycogen is insufficient to accommodate the intake, such as in cases where high calorie diets have been consumed for very long periods of time so that glycogen and triglyceride levels are nearly maximal in adipose, liver, and muscle tissue.

Conclusion

A dynamic semi equilibrium steady state that is normal, where blood glucose is within the normal range that does not cause glycation of proteins such as HbA1c, may be compared to a river that is not in a storm. Here the water level is normal since the water input matches the water output. But during a storm where storm water surges into the river, the river water level swells. This new steady state dynamic system is at a near equilibrium condition, but nevertheless the river being swelled

means it is not normal. A heavier storm that causes the river to swell to overflow the banks can produce acute effects. Likewise, a high caloric diet for a long time so that storage is impaired leads to elevated blood glucose levels that are not normal. When prolonged, this leads to glycation of protein and functional abnormality that can no longer be reversed. This occurs in long standing type II diabetes with microangiopathy in nerves and blood capillaries, typically after a 10 year period of hyperglycemia. If even higher caloric intake occurs, then the glucose level can swell to exceed the renal threshold and spill into the urine. This is the hallmark condition in type I diabetes due to insulin lack but is not common in type II diabetes. As previously stated, to correct the metabolic condition in type II, it is necessary to reduce caloric intake until blood glucose returns to a normal range, and then to eat an isocaloric diet from that time forward. These concepts are in full agreement with the recent discussions reviewed by Williams and Wu on the syndrome referred to as over-nutrition [20].

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