How Does Bariatric Surgery Cure Type II Diabetes? The hypothesis of a pathogenic insulin analogue that interferes with the function of endogenous insulin causing insulin resistance and NIDDM

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This hypothesis proposes the existence of a Pathogenic Insulin Analogue (PIA), which is absorbed in the proximal gut and interferes with the insulin binding receptors, preventing the normal function of endogenous insulin. PIA, causes or substantially contributes to, the development of impaired glucose tolerance, insulin resistance, and non-insulin-dependent diabetes mellitus (NIDDM). PIA is produced by the intestinal microbiota in the proximal gut in the presence of food. Bariatric surgery is effective in curing NIDDM because it prevents food entering the proximal gut (stomach, duodenum, jejunum), hence stopping the formation and absorption of PIA resulting in lasting remission of NIDDM.

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Background
There is a constellation of symptoms and pathologies: late-onset diabetes mellitus, NIDDM, insulin resistance, metabolic syndrome X, etc. in which a dysfunction of insulin metabolism is evident. Insulin affects most tissues and organs through its control of oxidative glucose metabolism. NIDDM is presently of unknown aetiology. Co-morbidities include obesity, hypertension, sleep apnoea, arthritis, retinopathy, infertility etc.

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The demand for bariatric surgery, especially for gastric bypass procedures, is increasing exponentially (3) without an understanding of how it cures NIDDM within days (4). In fact, an estimated 205,000 bariatric surgical procedures were performed in the United States in 2007. The cure is so rapid and total that all medications for diabetes can be set aside days after the operation. The cure is lasting; a recent meta-analysis of 22,094 patients showed that 84% experienced complete reversal of type 2 diabetes mellitus.

I have reviewed the relevant literature and tested it against the postulate that there exists a Pathogenic Insulin Analogue (PIA) which is absorbed in the proximal gut that interferes with insulin binding receptors, preventing the normal function of insulin.

If this hypothesis is proven to be true, it would explain much anecdotal evidence about low-carbohydrate diets and their health effects, and initiate research not only for the prevention and treatment of NIDDM but also for other age-related, degenerative, and late-onset diseases.

The Hypothesis
A survey of medical literature did not reveal Pathogenic Insulin Analogue Hypothesis Barabás
Bariatric surgery operations were developed to treat morbid obesity but they were found to cure NIDDM (7-11). The effectiveness of bariatric surgery (especially RYGB and BPD) indicates that the proximal gut (the stomach, duodenum and proximal ileum) is a significant contributor to the pathology of NIDDM.

Postoperatively, as summarised by Pories et al. (12):
• All the symptoms of NIDDM vanished within days of the operation.
• The cure is so total that all medications for diabetes can be set aside days after the operation.
• The cure is lasting.
• The appetite of the patients is permanently reduced; they became satiated earlier and remained so long after the postprandial period.
• The blood lipid balance improves.
• The gastric bypass also corrects or alleviates co-morbidities such as obesity, hypertension, sleep apnoea, cardiopulmonary failure, arthritis, and infertility.

The abrupt cure negates beliefs that NIDDM is a “lifestyle disease”, that obesity per se is the cause of it, or that the cause is the lack of exercise. This is because NIDDM is cured within days of bariatric operations, long before there is a significant change in the corpulence, or the physical fitness of the patients. The absence of food in the proximal gut seems to be an essential requirement. Pories et al. also described one case where the patient had a sham operation only, followed by a postoperative “nothing-by-mouth” feeding period. On the operating table, food was present in the patient’s stomach, so the planned bariatric operation was aborted. Postoperatively, the patient was fed only intravenously, during which time he had a remission of NIDDM. I believe that it was the absence of food in the proximal gut that caused the remission. Once all the food had passed through the proximal gut during the postoperative “nothing-by-mouth” period and was not replenished, the enteric flora in the proximal gut stopped producing PIA, so none entered the bloodstream. During the following days, the blocked insulin receptor sites cleared, insulin regained access to the previously blocked binding sites and activated glucose transport, and NIDDM symptoms vanished. After four weeks when food was taken orally again, the gut flora soon returned, PIA was produced once more and the symptoms of NIDDM re-emerged. This case history corroborates the PIA hypothesis that food in the proximal gut is needed as a substrate to produce PIA.

Dieting usually means eating fewer carbohydrates and eating lots of vegetables. Thus, the observed beneficial effects of a low-carbohydrate diet may be the result of reduced production of PIA. PIA may not be inactive metabolically. It may be depleted or cleared during physical exercise, so vigorous exercise would help to open up previously blocked sites and make them available for the circulat-
ing insulin, thus helping glycohomeostasis. I believe that the amount of glucose that can be cleared by the body in a given time depends not only on the amount of insulin in the blood but also on the available functioning insulin binding sites. The body (liver, muscles, etc.) has a fixed number of insulin binding sites that can play a part in glucose regulation, so the body’s total capacity is set. In NIDDM, a portion of these sites is deactivated by PIA; hence, the body’s ability to clear glucose is reduced no matter how high the insulin level is in the blood. When the residual glucose clearance capacity becomes insufficient to cope with the glucose entering the blood, the blood becomes hyperglycaemic. High blood glucose levels stimulate insulin release from the pancreas. Thus, the classical clinical picture of insulin resistance emerges: hyperglycaemia co-existing with hyperinsulinaemia. The severity of the impairment of glucose tolerance depends on how many binding sites are disabled and how many remain functional. If the decline in glycaemic homeostasis is small but is challenged by too much of the wrong food, hyperglycaemia can become overt sooner.

The response to PIA by diverse tissues such as fat cells may vary. Some may be more susceptible to interference by PIA than others. For instance, the omental fat may accumulate more in NIDDM than other fat deposits (13). The clinical correlation between the girth of the waist and the severity of NIDDM would be explained by that difference in response to PIA.

Alterations in gut hormones after bariatric surgery have been much studied, but fail to account for the observed changes. Cholecystokinin, serotonin and vasoactive intestinal peptides were found to be unaffected by gastric bypass operations. IGF-I levels were significantly lower in operated patients compared to non-operated obese women (14). In morbidly obese adults, after bariatric surgery the fasting Peptide YY levels increased and Glucagon-like peptide-1 (15) concentrations decreased independently of each other (16), and ghrelin levels in the blood, likewise, do not explain the profound effects on hunger (17).

Bariatric surgery affects the onset of satiety and lessens appetite. Cunningham et al. (18) note in their review article that there is a “profound loss of appetite that typically results from RYGB,” the most successful bariatric operation. This decrease in hunger is not explained by early satiety from gastric restriction alone because it extends well beyond the immediate postprandial period. Because of the reduced functional gastric capacity, post-RYGB patients are expected to experience early satiety, and eat smaller meals. “If this were the only mechanism at work, the energy homeostasis system would drive patients to compensate with increased meal frequency and to favor calorie-dense foods in response to massive weight loss. Instead, people who have undergone gastric bypass paradoxically
Leptin is produced by adipose tissues and acts on the ventral medial nucleus of the hypothalamus known as the “satiety center”. Binding of leptin to this nucleus signals to the brain that the body has had enough to eat. However, contrary to expectations, both leptin levels and appetite decrease following bariatric surgery (20), so it is not the leptin level in the blood that directly regulates hunger in NIDDM. PIA may affect receptors in the hypothalamus in the same way it affects insulin receptors in muscle and adipose tissues: by blocking them. The partially obstructed receptors in the hypothalamus might then allow less leptin to bind, so these individuals will feel less satiation and compulsive eating (hyperphagia) can result. The two contemporary world epidemics, obesity and diabetes, may very well be related and interconnected in this manner.

Evaluation of the Hypothesis
Whether more PIA is produced in NIDDM, or simply a larger proportion of what is normally produced is absorbed, needs to be investigated. Importantly, the organisms producing PIA need to be identified and measures to neutralize them investigated. For example, metformin, a biguanide antidiabetic medication that has been in use for over 30 years in the treatment of NIDDM (alas its mechanism of action remains unknown), may act as a suppressor of the relevant intestinal flora. The finding that metformin decreases intestinal glucose absorption in a dose-dependent manner (21) together with the often observed side effect of metformin gastrointestinal upset, (diarrhoea, cramps, nausea, and vomiting) imply an interference with the existing enteric flora, reminiscent of how broad-spectrum antibiotics cause similar upsets. Also, the weight loss that is observed in patients taking this drug may be a direct result of metformin changing the gut flora itself.

It is possible that broad-spectrum antibiotics given orally (for example, antibiotics prescribed for periodontal disease) may function to temporarily suppress the relevant intestinal flora, producing transitory remission. Although the long term use of these antibiotics could promote drug resistance, this explanation would corroborate the observed causative relationship between the gut flora and NIDDM.

Incessant consumption of sweetened drinks and refined carbohydrates in the modern diet create an altered environment throughout the alimentary canal.

Recently, the spread of NIDDM, obesity and other co-morbidities have been referred to as an epidemic. Indeed, it might be that a virulent strain of microorganism evolved in the recent past and is now spreading in the population. Incessant consumption of sweetened drinks and refined carbohydrates in the modern diet create an altered environment throughout the alimentary canal. Darwinian evolution would imply that this new food source would select for microorganisms proficient in utilizing it.

Some experiments that would corroborate this hypothesis
- At the time of the bariatric operation, microbial samples should be taken of the content of the proximal gut and at
various times postoperatively. These should be tested for the type and amount of strains present.

- Also the content of the gut should be tested for the presence of insulin and insulin analogues.
- The effects of broad-spectrum antibiotics taken by patients with NIDDM should be collected and scrutinised for possible remission.
- Germ-free experiments with NIDDM-prone mice would confirm the importance of the intestinal biota.
- Intravenous-feeding-only of patients with NIDDM may confirm that the presence of food in the proximal gut is needed to sustain the symptoms of NIDDM. This would reproduce the case reported by Pories et al. previously mentioned in this paper.
- Metformin-containing agar and controls need to be compared in Petri dishes for their ability to support the growth of intestinal microbial flora.
- Intravenous metformin injected into the portal vein in diabetic animals may be tried to see if metformin directly affects liver metabolism.
- Identifying PIA in the portal vein would be the final proof.

References
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