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A novel cobiotic containing a prebiotic and an antioxidant augments the glucose control and gastrointestinal tolerability of metformin: a case report

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CASE REPORT

Abstract

The gut microbiome plays an important role in regulation of metabolic processes, including digestion, absorption, and synthesis of bioactive molecules that signal physiological host mechanisms. Changes in the human gut microbiome are associated with type 2 diabetes and insulin resistance. Water-soluble dietary fibres like inulin and beta-glucan are fermented in the colon, and beta-glucan increases viscosity. Blueberries improve insulin sensitivity through an antioxidant effect. A cobiotic, consisting of purified inulin, sugar-free blueberry pomace extract, and an oat preparation of purified beta-glucan was developed for twice a day (bid) consumption as a smoothie drink to repair the gastrointestinal dysbiosis in type 2 diabetes. A 30-year-old man presented with new onset type 2 diabetes and a fasting glucose (FBS) of 375 mg/dl. Metformin 500 mg bid was initiated and increased to 1 g bid after 1 week. During the first 9 days of metformin treatment, he developed diarrhoea, but his FBS only dropped to 325 mg/dl. The cobiotic bid was added on the 9th day of metformin treatment, and after 2 days, his FBS dropped to 175 mg/dl. After 8 weeks on metformin and the cobiotic, his blood sugar was 100 mg/dl and he lost 5.5 kg. His stools became soft and formed on the cobiotic, reverted to diarrhoea when off of it for 2 days, and returned to normal on resuming the cobiotic formulation. Metformin is a safe, effective and inexpensive generic medication favouring weight loss, recommended as initial treatment of type 2 diabetes by the American Diabetes Association. However, a 20% incidence of diarrhoea limits its tolerability. A safe food supplement that can increase the efficacy of metformin and its tolerability, as occurred in this case report, would have significant positive public health consequences. A controlled clinical trial of the cobiotic with metformin is planned.

Keywords: beta-glucan, inulin, diarrhoea

1. Introduction

The human gut microbiome appears to be involved in the regulation of metabolic processes, including digestion, absorption, and conversion of indigestible foods or partially digested food ingredients to molecules that may signal physiological host mechanisms. The gut microbiome is a complex ecosystem. A change in that habitat may result in microbiota community shifts and consequential changes in glucose regulation (Qin *et al.*, 2012). Recently, analysis of faecal microbiota showed that patients with type 2 diabetes have a moderate degree of gut microbial dysbiosis, a decrease in the abundance of some universal butyrate-producing bacteria and an increase in various opportunistic pathogens, as well as an enrichment of other microbial functions conferring sulphate reduction and reduction of oxidative stress resistance (Qin *et al.*, 2012). Other studies showed that obesity, type 2 diabetes, insulin resistance and the related metabolic syndrome are closely associated with a low-grade inflammation, in which the gut microbiota play a very important role (Cani *et al.*, 2008; Licht *et al.*, 2006; Pendyala *et al.*, 2012; Turnbaugh *et al.*, 2006; Vijay-Kumar *et al.*, 2010).

Inulin is a water soluble dietary fibre that increases the abundance of butyrate in the colon through fermentation

(Licht *et al.*, 2006). Beta-glucan is also fermented in the colon (Beckmann *et al.*, 2006), yet beta-glucan's physical properties tend to increase viscosity of the digesta (Dikeman *et al.*, 2006). High viscosity delays gastric emptying (Juvonen *et al.*, 2009; Marciani *et al.*, 2000) and slows digestion and absorption of nutrients (Isaksson *et al.*, 1982). Bioactivities of inulin and beta-glucan in the gastrointestinal (GI) tract are proposed to account for an increase in post-prandial satiety in response to a standard meal, reduce the glucose and insulin response to a breakfast meal, reduce the glycaemic index, increase fasting peptide YY and glucagon-like peptide-1, decrease ghrelin levels, reduce body weight, and increase insulin sensitivity in humans (Bays *et al.*, 2011; El Khoury *et al.*, 2012; Greenway *et al.*, 2007; Vitaglione *et al.*, 2009). Blueberry pomace extract contains polyphenols and anthocyanins, which are poorly absorbed (Manach *et al.*, 2004), but alter the GI microbiome to improve insulin sensitivity in obese insulin-resistant men and women (Stull *et al.*, 2010). A formula containing all three bioactive food ingredients (inulin, beta-glucan and blueberry extract), here called a cobiotic because it is not metabolised or absorbed in the upper GI tract, presents to the colon where it has the potential to change the composition of the GI microbiome and thus the activity or abundance of specific GI microbiota. It is hypothesised that the cobiotic may change the ecosystem by providing a micro-setting to augment gastrointestinal tolerability of metformin and correct the dysbiota recently reported in type 2 diabetics.

Based on these inherent properties of inulin, beta-glucan and blueberry pomace extract, a cobiotic was formulated (NM504, NuMe Health LLC, New Orleans, LA, USA) to be consumed as a smoothie drink twice a day. A randomised clinical trial is in progress to evaluate the effect of this cobiotic on the gut microbiome, insulin sensitivity and anorexigenic gut hormones in subjects with impaired fasting glucose. We observed one diabetic subject consuming the cobiotic with metformin. The effect of NM504 on glucose metabolism and the tolerability of metformin will be described in the following case report of a newly diagnosed diabetic subject.

2. Case report

JH, a 30-year-old Caucasian male, gained 10 kg over 8 months and developed lower back pain. He presented to his primary physician with that complaint. At the time of his presentation, the patient was taking omeprazole (20 mg/d) for gastrointestinal reflux disease in addition to lisinopril (40 mg/d), metoprolol (100 mg/d) and hydrochlorothiazide (25 mg/d) for hypertension. He had no allergies and had undergone no surgeries. He denied past hospitalisations, trauma with residua or blood transfusions. He drank 3-4 alcoholic drinks per week on average but had never smoked, and had no history of intravenous drug use. He was a full-time law student and had no exposures to occupational toxins. Prior to his presentation, he had been sexually active with one woman in the past 6 months. The patient's mother and father were living and well. He had one sister who was living and well, and he had no children. There was no family history of diabetes. He had no complaint other than lower back pain. On physical examination, he was 104 kg with a height of 165 cm and a body mass index of 38.3 kg/m^2. His blood pressure was 116/70 mmHg with a pulse rate of 80/min, and he was afebrile. Urinalysis demonstrated presence of glucose, followed-up with a non-fasting capillary blood glucose of 450 mg/dl, a haemoglobin A1c (HgbA1c) of 8.8%, and a microalbumin to creatinine (M/C) ratio of 147.

His physician made the diagnosis of type 2 diabetes mellitus based on his age, lack of acidosis and fasting blood sugar of 375 mg/dl. He was started on metformin 500 mg twice a day and was instructed to measure his fasting blood sugar on a daily basis. Over the course of 7 days, he was instructed to increase metformin to 1000 mg twice a day. Over the course of the 9 days of metformin treatment, he developed watery stools and his fasting blood sugar only dropped from 375 mg/dl to 325 mg/dl. He knew from his contact with NuMe Health that the company was developing and testing a dietary supplement with a goal of increased insulin sensitivity through a salutary effect on the stool microbiome. On the 9th day of his treatment with metformin, he added the cobiotic formulation as a smoothie drink taken twice a day, within an hour before breakfast or lunch and within an hour before dinner. Within two days of starting the cobiotic, his fasting glucose dropped from 325 mg/dl to 175 mg/dl and after 8 weeks of taking the formulation along with the metformin, his fasting blood glucose was 100 mg/dl (Figure 1). By week 10, his HgbA1c was 6.3% and his M/C ratio was 16. Dividing the first 60 days of diabetes treatment into 10 day periods, his blood sugar and its variance (mean±standard deviation) decreased from 344±44.1 mg/dl in the first 10 days, to 182.2±14.7 in the second 10 days, 144.3±9.6 during the third 10 days, 114.5±11.8 during the fourth 10 days, 123.0±9.6 during the fifth 10 days, and 121.0±11.8 during the sixth 10 days (Figure 2). During this period, his weight decreased 5.5 kg, while his watery stools reverted to soft regular formed bowel movements. After an additional month, he ran out of the cobiotic for 2 days. During that period, his blood sugar increased from 100 mg/dl to 131 mg/dl and his diarrhoea returned. After resuming the cobiotic, his blood sugar returned to 121 mg/dl and his stools returned to being formed and soft. His diabetes and stools have remained under control on the combination of metformin and the cobiotic formulation at the time of this writing.

3. Discussion

Although the definitive clinical trial of NM504 is still in progress, this case report is encouraging in regards to the trial's success. Not only did the cobiotic appear to have a

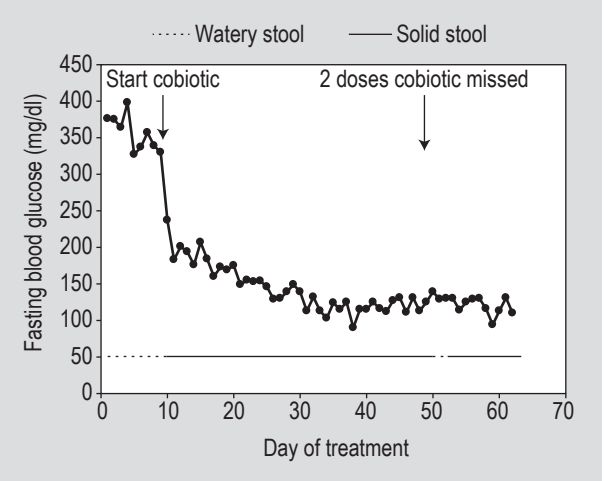

Figure 1. Fasting blood sugar during the first 60 days of type 2 diabetes treatment, first with metformin 1000 mg twice a day and then with metformin 1000 mg plus cobiotic formula NM504 twice a day. The combination was continued except from days 49 to 51, when daily dosing of NM504 was missed. Diarrhoea was associated with metformin, except when NM504 was added.

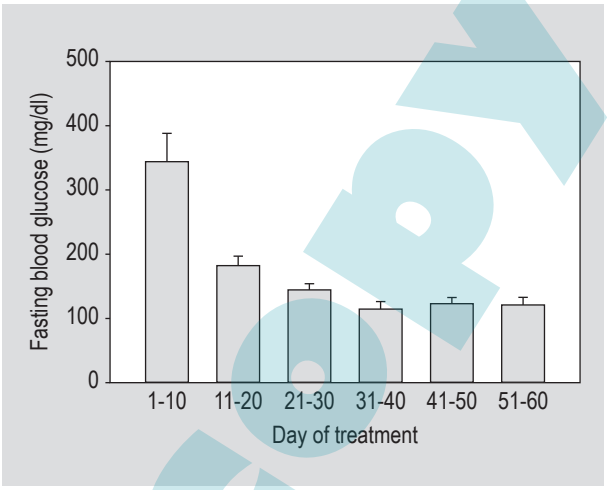

Figure 2. The first 60 days of treatment for newly diagnosed type 2 diabetes. The first 10 days were on metformin 1000 mg twice daily and the remainder on metformin 1000 mg plus cobiotic formula NM504 twice daily, showing a decrease in fasting blood sugar and blood sugar variability (1 standard deviation) over time.

positive effect on fasting blood sugar, but the watery stools induced by treatment with metformin were normalised. This is a potentially important clinical observation. Metformin is the preferred initial drug of choice for the treatment of type 2 diabetes and is included as such in most diabetes treatment guidelines (Anonymous, 2012; DeFronzo and Abdul-Ghani, 2011; Goldberg *et al.*, 2009; Inzucchi *et al.*, 2012). However, it is reported to cause a 20% incidence of diarrhoea in diabetic patients taking the drug compared to only 6% of diabetic patients not taking metformin (Dandona *et al.*, 1983). In fact, diarrhoea with metformin is a sufficient problem that some diabetic patients have to discontinue its use due to the intolerability. Metformin has a great safety and efficacy record, causes an approximate 2-3 kg weight loss, reduces the conversion of impaired glucose tolerance to diabetes, reduces cardiovascular risk factors, and is a low-cost generic medication. Therefore, by increasing the tolerance to metformin while increasing its efficacy, the safe cobiotic medical food would have excellent beneficial public health consequences.

A double-blind, randomised, controlled clinical trial is now in progress to evaluate the effect of the cobiotic on insulin resistance, stool microbiome and anorexigenic gut hormones in people with impaired fasting glucose. This case report suggests that a clinical trial testing the effect of the cobiotic in type 2 diabetic patients taking metformin would be another important study to perform. It is hoped that such a clinical trial would confirm an improvement in glucose control and lower gastrointestinal side effects of metformin when combined with the cobiotic, allowing more type 2 diabetic subjects to take metformin and increasing the effectiveness of metformin simultaneously.

Acknowledgements/conflicts of interest

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