Prevalence of Idiopathic Reactive Hypoglycaemia and Impact of Fructo-Oligosaccharide Supplementation on Blood Glucose Variability

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ABSTRACT

BACKGROUND:

The term *idiopathic reactive hypoglycaemia* (*IRH*) applies when a meal-induced dip in blood glucose, or symptoms of hypoglycaemia, follows high-starch, low-fibre meals in otherwise healthy individuals. Due to inconsistency of its definition and debated clinical value, reported prevalence of this state varies. No consensus exists on optimal treatment of IRH, hence we wanted to investigate 1) the prevalence and characteristics of IRH, and 2) if diet supplementation of fibre could improve the reactive glucose response in IRH.

METHODS:

362 subjects (71 ± 9 years, 146 females), all previously undiagnosed of dysglycaemia, who had participated in on of two case-control studies involving a oral glucose tolerance test (OGTT), were classified according to WHO standards (type 2 diabetes mellitus (T2DM), impaired glucose tolerance (IGT), normoglycaemia (NGT)) or categorized as IRH if OGTT 1h- or 2h- capillary blood glucose (cBG) levels were ≤ 3.9 mmol/L or 1h- or 2h- glucose were < fasting cBG, with no evidence of T2DM or IGT. Characteristics of the IRH group were aligned with T2DM, IGT and NGT groups through a case-control evaluation of lipids, inflammatory- and IGF system parameters, cardiovascular complications, medications and anthropometric measures.

Further, twelve (56 ± 8 years, 6 females) subjects from the IRH minority were recruited in a 4-week, randomized, crossover intervention, to evaluate the glucometabolic and anthropometric effects of fructo-oligosaccharides (FOS), a dietary soluble fibre with texturising properties (10g bid for 2 weeks, no treatment the following 2 weeks). At the end of each 2-week treatment sequence, fasting laboratory samples, a 4h-OGTT (blood glucose (BG) measures every 30th minute) and anthropometric measures were conducted.

RESULTS:

IRH was found in 12.4% of the subjects whom characteristics were: younger, a more favourable inflammatory- and IGF system axis profile and lower coronary artery disease (CAD) prevalence, compared to all other groups.

FOS leveraged a significant improvement in several of the glucometabolic parameters. Although some fasting parameters were significantly reduced (plasma glucose and total cholesterol

levels; 5.4 $\pm$ 0.6 vs. 5.1 $\pm$ 0.5 mmol/L, $p \leq 0.05$ and 5.3 $\pm$ 1.1 vs. 4.9 $\pm$ 1.1 mmol/L, $p \leq 0.04$, respectively), most benefits were seen in the 4h OGTT trajectory during the last two hours of the 4h-OGTT. FOS significantly reduced glycaemic exposure (AUC) between 180 and 210 minutes ($p = 0.03$) and reduced the proportion of capillary blood glucose measurements $\leq$ 3.9 mmol/L from 21 to 11($\chi^2 = 4.26$, $p = 0.04$) in this period. Moreover, favorable alternations in the shape of the OGTT curve were seen, with less pronounced zeniths and nadirs.

CONCLUSION:

A reactive hypoglycaemic response during an OGTT is prevalent in older adults and this phenomenon could be modulated by dietary supplementation of FOS. The stabilizing effects of fructo-oligosaccharides on blood glucose should be assessed in patient groups where BG variability plays a role, e.g. in T1DM or T2DM.

SAMMENDRAG

TEORI:

Idiopatisk reaktiv hypoglykemi (IRH) beskriver tilstanden der inntak av matvarer med mye stivelse og lavt fiberinnhold, hos ellers friske personer, fører til et fall i glukosekonsentrasjonen, eller symptomer på hypoglykemi oppstår. Definisjonen av IRH og den kliniske viktigheten er debattert, det er heller ingen enighet om optimal behandling. Vi ville derfor studere 1) prevalensen og karakteristika ved IRH, og 2) om tilskudd av fiber kunne forbedre den reaktive glukoseresponsen som ses ved IRH..

METODER:

362 personer (71 $\pm$ 9 år, 146 kvinner), der ingen hadde diagnostisert dysglykemi og som hadde deltatt i en av to case-kontrollstudier hvor oral glukosetoleransetest (OGTT) inngikk, ble klassifisert i henhold til WHO-standard (type 2 diabetes mellitus, nedsatt glukosetoleranse (IGT), normal glukosetolerant (NGT) eller kategorisert med IRH (1- eller 2-timers glukosenivå $\leq$ 3.9 mmol/L eller 1- eller 2-timers glukose < fastende glukose med fravær av T2DM eller IGT). I en case-kontrollanalyse av lipider, inflammatoriske- og IGF akse-parametere, kardiovaskulære komplikasjoner, medikamenter og antropometriske verdier, ble IRH-gruppen sammenliknet med personer med T2DM, IGT og NGT .

Videre ble tolv personer (56 $\pm$ 8 år, 6 kvinner) fra gruppen klassifisert med IRH rekruttert til en 2-ganger-2 ukers, randomisert crossover intervensjon for å evaluere 20 g/dag frukto-oligosakkarider (FOS) sin effekt på glykometabolske- og antropometriske verdier. Fastende blodprøver, 4-timers OGTT (med kapillære glukosemålinger hvert 30. minutt) og antropometriske målinger ble gjennomført avslutningsvis i hver 2-ukers periode.

RESULTATER:

IRH ble funnet hos 12.4% av deltagerne, som også var yngre, hadde en gunstigere inflammatorisk- og IGF system akseprofil og en lavere forekomst av koronar arteriesykdom (CAD), sammenliknet med de andre gruppene.

Inntak av FOS førte til en signifikant forbedring av flere glykometabolske parametere. Fastende plasmaglukose og totalkolesterol ble signifikant redusert (henholdsvis 5,4 $\pm$ 0,6 mot 5,1 $\pm$ 0,5 mmol/L, $p \leq 0,05$ og 5,3 $\pm$ 1,1 mot 4,9 $\pm$ 1,1 mmol/L, $p \leq 0,04$), og under de to siste timene av

4-timers OGTT, observerte vi et signifikant redusert glukoseareal under kurven (AUC) mellom 180 og 210 minutter ($p = 0,03$) og et signifikant redusert antall kapillære glukosemålinger $\leq 3,9$ mmol/L fra 21 til 11 ($\chi^2 = 4,26$, $p = 0,04$). Samlet sett ble OGTT-kurven mer utflatet etter FOS-inntak når senit- og nadir-nivåer ble sammenlignet mot perioden uten FOS.

KONKLUSJON:

En reaktiv hypoglykemisk respons under OGTT forekommer i eldre voksne og FOS-supplementering kan i slike tilfeller være gunstig. Den blodsukkerstabiliserende effekten av FOS bør evalueres i pasientgrupper der glukosevariabilitet spiller en rolle, som ved T1DM og T2DM.

CONTENTS

ABBREVIATIONS

ABAF	Asker and Baerum Atrial Fibrillation
BG	Blood glucose
BMI	Body mass index
CGMS	Continuous glucose monitoring system
CTR	Control
CV	Cardiovascular
DM	Diabetes mellitus
fcBG	Fasting capillary blood glucose
FOS	Fructo-oligosaccharides
GABI	Glucose ABnormality in Ischemic cardiovascular conditions
GIP	Glucose-dependent insulinotropic polypeptide
GL	Glycaemic load
GLP-1	Glucagon-like peptide 1
HbA1c	Haemoglobin A1c
HDL	High density lipoprotein
IFG	Impaired fasting glycaemia
IGT	Impaired glucose tolerance
IRH	Idiopathic reactive hypoglycaemia
LDL	Low density lipoprotein
OGTT	Oral glucose tolerance test
T2DM	Type 2 diabetes mellitus
TG	Triglycerides

1. INTRODUCTION

Blood glucose (BG) values below lower levels of normal defines hypoglycaemia and in subjects with diabetes mellitus (DM) who receives glucose-lowering drugs, this cut-off, according to the American Diabetes Association, is ≤ 3.9 mmol/L (1). In subjects without DM however, the hypoglycaemia cut-off value is not generally agreed as indicated with proposals ranging from < 2.5 mmol/L (2) to 3.9 mmol/L (3). This may be due to that the level of glycaemic thresholds for secretion of counterregulatory hormones and onset of physiological, symptomatic, and cognitive changes in response to hypoglycaemia in non-diabetic humans, is not uniformly reported, and may be dependent on setting of which this is measured (2). Furthermore, the diversity of the conditions, with their different aetiology, that are known to cause such (Table 1) also could contribute to this lack of consensus (5).

1.1 Idiopathic reactive hypoglycaemia (IRH)

One specific hypoglycaemic phenomenon is the so-called reactive hypoglycaemia (RH), which is a time-related and meal-induced syndrome that is characterized by the Whipple's triad (i.e. 1: Symptoms, signs, or both consistent with hypoglycaemia, 2: A low plasma glucose concentration, 3: Resolution of symptoms or signs with raised plasma glucose) (2). Classically this manifest in patients that have submit to gastric (dumping phenomenon) or bariatric surgery (interferes with incretin hormones) (6). However, in the case of RH, in apparently healthy individuals experience to five hours subsequent to high starch – low fibre meals, with an overall high glycaemic load (GL), in the absence of DM or known disease conditions in which this is known to be associated with (Table 1), and without fulfilment of the Whipple's triad, this is termed idiopathic reactive hypoglycaemia (IRH) or idiopathic postprandial syndrome (7).

The definition of IRH is not agreed. It was originally described by Harris who suggested in 1924 this condition to relate to postprandial glucose values < 4.0 mmol/L (8). Brun et al. (6) later suggested a cut-off of < 3.3 mmol/L, while Marks & Teale, rather than relating cut-off values to meal, defined IRH to plasma glucose levels of less than 3 mmol/L during the standard oral glucose tolerance test (OGTT) (9).

IRH is by some not regarded as a disease entity (10, 11), which might be related to absent symptoms corresponding with biochemical hypoglycaemia (12). However, the prerequisite in literature for BG to be ≤ 3.3 mmol/L during symptoms for to classify IRH may be too limited since after consumption of a high glycaemic-index breakfast individuals prone to IRH have reported

symptoms at higher BG level (4.40 ± 0.83 mmol/L) than traditional threshold values (13) and several studies shows that symptoms of hypoglycaemia do not correspond to measured plasma glucose (14, 15). Three studies, from UK, Canada and Denmark, e.g. found that only 23%, 47% and 0%, respectively, of study subjects had plasma glucose values ≤ 3.3 mmol/L and simultaneously symptoms of hypoglycaemia (16-18).

Moreover, study subjects are usually semisupine during protocols used to investigate symptom thresholds, whereas it has been shown that symptoms and physiologic responses to insulin-induced hypoglycaemia are increased when upright (19), therefore, symptom thresholds, defined by hyperinsulinemic clamp studies, may underestimate hypoglycaemia in free-living, ambulatory individuals.

1.2 Prevalence of IRH

The reported prevalence of IRH varies due to non-agreement in the diagnostic practice and the difficulty in identifying the aetiology and the fact that probably the majority of subjects reporting this problem do not have a biochemical hypoglycaemia after conventionally comprehensions/ appraisals (20). In a British trial among 1136 randomly chosen women aged 17-50 years, self-reported symptomatic hypoglycaemia occurred among 37.9% four times monthly (21). In selected populations it may even be higher, as a prevalence of 30 and 50% is reported in type 2 DM (T2DM) and in lean, young women with polycystic ovary syndrome, respectively (22, 23). This indicates that a substantial number of subjects are affected by IRH, and from lessons learned from hypoglycaemia occurring in DM (24), this might have a deleterious impact on health-related quality of life (HRQL) (25).

Postprandial hypoglycaemia has been popularized in the media and lay literature and in several countries the number of persons being referred for medical assessment of this condition is high (10, 21). The syndrome is alleged to be more prevalent among lean people with a low fat percent (6, 21), possibly due to that slimming increases insulin sensitivity (26) and that during increased glucose processing by exercise, there is frequently observed cases of exaggerated decrease in blood glucose. Such antecedent hypoglycaemia during the preceding day can blunt neuroendocrine glucagon, insulin and catecholamine responses as well as endogenous glucose production, lipolysis and ketogenesis and by this, impairing defences against exercise hypoglycaemia (27).

It has also been noted a higher prevalence of IRH in women, possibly due to the sexual

dimorphism in counterregulatory responses to hypoglycaemia where plasma glucose values would have to fall to a lower level in women before release of counteracting hormones take place compared to in men (28) with a 44% and 17% lower epinephrine and norepinephrine response, respectively (29) and a twofold greater glucagon response in men relative to women (30). This was also seen in a study examining the shape of the curve during an OGTT (31), where biphasic curves was observed more frequently and more pronounced in women than in men. The latter study found genetic variations to be involved too, where homozygosity of the cysteine protease calpain 10 (CAPN10 UCSNP44) allele was associated with a monophasic shape.

1.3 Bio-pathological explanation for IRH

Although there are several symptoms due to hypoglycaemia, the most frequently observed can be grouped as either autonomic (i.e., sweating, warmth sensation, anxiety, nausea, palpitation and hunger) (32) or related to neuroglucopenia (i.e., tiredness, being uncoordinated, visual disturbances, drowsiness, altered behaviour, confusion, and, if left untreated, coma and seizures), caused by glucopenia in the brain (33). The autonomic symptoms tend to occur first, at a blood glucose level of around 3.3–3.6 mmol/L and neuroglucopenia at lower levels, e.g. < 2.6 mmol/L (20). Hence, glycaemic thresholds for activation of an autonomic endocrine response are higher than those for the development of symptoms and impairment of cognitive function (6). The classical hierarchy for this in subjects without diabetes is illustrated in Figure 1.

To maintain glucose homeostasis the body requires mechanisms to respond to the intermittent provision of nutrients and intervals of no nutrient supply. In healthy persons postabsorptive euglycaemia is regulated within approximately 3.3 to 5.6 mmol/L despite intermittent ingestion of food (34). Insulin is the chief modulator of keeping this balance, and its secretion from pancreatic islet β-cells is stimulated by enteric incretins following ingestion of nutrients. In the postabsorptive state glucagon secreted from the pancreatic islet α-cells stimulates glucose production and provides the primary defence against hypoglycaemia, but has no effect on extrahepatic glucose uptake (35). In the absence of glucagon, adrenomedullary epinephrine and the 10 times less potent norepinephrine, has an important role in the counterregulation by decreasing glucose utilization, increasing glucose production and reduce insulin secretion (36). Cortisol, on the other hand, is needed for normal glycogen synthesis and for the acceleration of glucose production by glucagon and epinephrine (6) and increments in plasma cortisol levels is seen in the late or profound hypoglycaemic phase together with increased secretion of growth hormone (19).

Irregularities in these hormonal- and/or cerebral mechanisms that otherwise tightly control the complex interplay of mechanisms involved in regulating BG level are one of the causations of IRH. This involves e.g., decreased or increased insulin secretion and/or defects in counterregulatory hormonal response (glucagon, epinephrine, norepinephrine, cortisol or growth hormone) (37) whether this affects secretion or receptor hypersensitivity (26). Basal glucagon is correspondingly reported to be significantly higher in subjects with IRH compared with normal subjects. During a 3-hours OGTT a paradox increase in plasma glucagon was noted in the IRH individuals together with a significantly delayed insulin peak, which might indicate an altered pancreatic α-cell function in these patients (35).

This is not the complete explanation though, because glucagon does not cause symptoms (but epinephrine does). The postprandial adrenergic response appearing after meals rich in carbohydrates and the rare association with low blood glucose level, could therefore be a result of higher beta-adrenergic sensitivity (17) or an earlier secretion of epinephrine in response to a falling blood glucose as has been reported in non-insulin treated T2DM patients (38).

Also involved could be disturbances in the entero-insular response with increased glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) (39). GLP-1 is secreted from the terminal ileum and colon L cells in reply to nutrients in the gut and is one of the most potent insulin stimulants (40). Although GLP-1 receptors are widespread in the body, in this context the gastric, hepatic and pancreatic ones are of most interest. This incretin inhibits gastric emptying and postprandial glucagon release (41), thus decreasing hepatic glucose production (1). GIP is secreted from K cells primary in the proximal small intestine. The GIP receptor is expressed in the pancreatic islet cells, adipose tissue, heart, pituary, adrenal cortex and several regions of the brain (42). As with GLP-1, this incretin stimulates insulin secretion and its secretion increases 10- to 20-fold above baseline values within minutes of ingestion of absorbable carbohydrates as well as lipids (40). Nauck and colleagues noted that approximately 50-70% of the insulin response to an OGTT can be attributed to the effect of incretins on the islet β-cells (39). Individuals with T2DM exhibit impairments in both GLP-1 and GIP secretion as compared to healthy individuals (43). Their impact on inducing hypoglycaemia however is limited, since they only exert an insulin-secretory stimulus in the presence of hyperglycaemia (44). However, since most cases of symptoms in IRH are in subjects without a biochemical low value, disturbances in this system also could play a role (45).

Notwithstanding, the most plausible explanation of IRH is probably attributed to high insulin sensitivity that is not adequately compensated by hypoinsulinemia (23). Hence with an endogenous hyperinsulinaemia, at least in relative terms, the dysfunction lies in the failure of

insulin to fall to very low rates as plasma glucose concentrations fall to hypoglycaemic levels, with the result of low rates of glucose production rather than high rates of glucose utilization (33). This is reflected in studies addressing the shape of the OGTT curve where a biphasic pattern with accentuated zeniths and nadirs seem to be present in subjects with IRH-like conditions (Figure 2) (31).

Interestingly, the shape of the glucose curve during OGTT may harbour metabolic information not captured by the level of glucose at present, e.g. glucagon secretion and sensitivity and hepatic glucose sensitivity. The shape of the BG curve has been categorized as 'monophasic', biphasic' or 'unclassified' (31) or 'domed' and 'upward' (46). Both insulin sensitivity and insulin secretion are involved as well as gastric emptying in the physiological processes contributing to the shape of the slope of the initial rise. Opposing this, OGTT features a non-physiological stress situation seldom encountered outside the clinical laboratory and induces a somewhat different glucose kinetic than a mixed meal (31) witch could give rise to false positive results (47). Instead it has been proposed to use a questionnaire (36), a classification of symptoms with a multifactorial analysis (48) or a breakfast test that mimics everyday habits and rules out artefacts as for the OGTT (49). By contrast, it is suggested that OGTT could still be employed for further investigation of relationships between symptoms and blood glucose values and in evaluation of glucose tolerance after the diagnosis has been made (48).

Conventional home blood glucose monitoring provides only a snapshot picture of prevailing glucose values and the gold standard seems to be ambulatory glycaemic measurements (6). The rationale for the use of this device is to detect unrecognised hypoglycaemia, especially at times when finger prick testing is difficult or impossible (e.g. at night). Subcutaneous glucose levels mimic blood glucose levels closely with a lag time of only a few minutes (50, 51). An investigation of 29 patients referred for a suspicion of a hypoglycaemic disorder with continuous glucose monitoring system (CGSM), found 46% of the symptoms to occur when BG < 3.3 mmol and 18% < 2.8 mmol (17). Since symptoms are not specific and OGTT is suggested not helpful in diagnosing IRH, frequent glucose measurements allows a personalized and more precise understanding of daily glucose fluctuations, giving the time and glucose levels followed by symptoms (52). Identification of glucose oscillations have been suggested to be a more reliable indicator of blood glucose control and risk for long-term complications than HbA1c alone (53), further are plasma insulin, GLP-1 and GIP responses found to be greater when a variable infusion of glucose is given, as is more representative for the situation in daily life, compared with a constant infusion in both healthy and T2DM patients (54).

1.4 Treatment of IRH

No specific recommendations for treatment have been proposed but in general, meal-related reactive hypoglycaemia should primarily be treated with dietary restriction of refined carbohydrates (55), frequent meals, and avoiding coffee and nicotine, although much controversy exists as to the optimal management of reactive hypoglycaemia (35, 49). Pharmacologic attempts in treating IRH involve potassium-channel activators (diazoxide) (6), biguanides (metformin) (56), α-glucosidase inhibitors (57), calcium-channel blockers, anticholinergic agents, phenformin (no longer widely available) (58), thiazolidinediones (glitazones), and somatostatin analogues (59). However, none of these medications are specifically indicated (60) and their long-term use in this indication has not been firmly established in controlled studies (61).

1.5 The potential impact of fibre on IRH

In people with frequent blood glucose variations, increased fibre intake for 24h is associated with a reduced postprandial glucose response on the following day (62). In fact, supplementing carbohydrate test meals with purified fibre has been shown to flatten the glycaemic response in healthy volunteers (63), to reduce urinary glucose loss, accelerate acute GIP- and insulin response (62) and improve diabetes control in subjects with DM (64). Involved in these advents may be the fermentation remnant and short-chain fatty acid (SCFA) acetate, that is capable of inhibit serum free fatty acid release from adipocytes (65), resulting in increased insulin sensitivity (64). Fibre also plays an important role in preventing T2DM (66) and reduce cardiovascular disease (CVD) risk and CRP levels (67,68). Longitudinal studies indicate an inverse association between dietary fibre intake and levels of inflammatory markers (69) such as interleukins (IL)-6, tumour necrosis factor alpha receptor-2 (TNF α-2R) (70) and CRP (69). IL-6 is probably the chief stimulant to hepatic production of CRP (71) and modulation of the cytokine milieu is possible with increasing the fibre content in meals (72), independently of body weight change (73). This is further emphasized when insulin, GIP, and GLP-1 responses to whole kernel rye bread is lower compared to consumption of white wheat bread (74). Dietary fibre may therefore play an important role in mediating the relation between diet, inflammation and cardiovascular disease (75) by way of altering the intraluminal bacterial environment witch contributes in the production of inflammatory cytokines (76).

A meta-analysis of 67 controlled trials that evaluated the role of dietary fibre on serum cholesterol indicated that high-carbohydrate diets, rich in soluble fibre (from oats, psyllium, pectin, and guar gum) decreases total- and low-density lipoprotein (LDL) cholesterol, with insignificant

effects on triglycerides and high density lipoprotein (HDL) cholesterol (77). Also, the fermentation products of fibres (including acetate) have shown to induce apoptosis of colorectal cancer cells (78), maintain mucosal respiration and growth (79) and synthesize folic acid, biotin and vitamin K (80).

Despite these only assorted mentioned mechanisms through which fibre in general can assist healthiness, the total consumption among the Norwegian population is far lower than the recommended 25 - 35 g/day (81, 82) with an estimated intake between 16 to18g/day (83). In other western societies consumption is even smaller (84), as for US with only 15 g/day (85).

1.6 Oligofructose

Inulin and oligofructose are linear β2-1 fructans (63) present in several fruits and vegetables (wheat, onion, banana, garlic, Jerusalem artichokes and chicory) (86) and their daily consumption has been estimated to 1-4g in the US (87) and 3-11g in Europe (86). Fructo-oligosaccharides (FOS) is made from chicory inulin which is enzymatically hydrolyzed to yield a degree of polymerization between 3 to 5 (Figure 3) (79). Oligofructose is resistant to hydrolysis by human small intestinal digestive enzymes, whereas being fermented by only a limited range of micro organisms in the proximal colon including the valuable, health promoting species bacteroides and bifidobacteria (88). Contrary, the concentration of fusobacteria and clostridia is suppressed (89), insinuating FOS to meet the criteria to be considered a prebiotic defined as: *A non digestible food ingredient that selectively stimulates growth and/or activity of one or a limited number of colonic bacteria, and thus beneficially improves host health* (89). Unlike the situation with probiotics, where allochthonous micro organisms are being introduced in the gut, and have to compete against established colonic communities, an advantage of using prebiotics to modify gut function is that the target bacteria are already commensally in various extents, to the large intestine. Thus, prebiotic supplementation seems to play a more important role in older individuals, e.g. > 55 years where faecal bifidobacterial counts are known to show marked decrease in comparison to those of younger persons (90)

By delaying gastric emptying (bulking effect) and retard nutrient absorption by trapping of low molecular weight carbohydrates in a viscous gel (89), oligofructose, together with a possible enhanced glucose utilization from colonic fermentation products of the fibre (47), could improve postprandial misbalance in the secretion of insulin and glucagon (91, 92).

A potential use of FOS in particular in IRH is supported by a 4 week study of 20g FOS/day or sucrose in 12 healthy volunteers that showed decreased basal hepatic glucose production after

FOS ($P < 0.02$) and an acetate-propionate ratio two times lower compared to lactulose in the volunteers faecal inoculums (91). This improved metabolism was related to the gluconeogenerator propionate, witch has been shown to inhibit gluconeogenesis from lactate and to stimulate glucolysis (92). Moreover, a crossover study with 30 subjects reported that intake of 10.6g/day of FOS in 2 months gave a significantly reduced postprandial insulin response (incremental area) after a standard test meal (protein 15%, carbohydrate 34%, fat 51%). On the other hand, the authors did not find any major effects on lipid metabolism (93) as seen in experimental models with rats, where FOS has been implied to lessen hepatic steatosis (94), presumably related to the dose-dependent response of functional fibres (95).

As in line with fibre in general, FOS also has been reported to reduce the risk of colon carcinogenesis, improve the bioavailability of essential minerals (magnesium and calcium) and reduce serum triglyceridemia by lowering hepatic lipogenesis (96).

1.7 Aims of the study

IRH, despite its limitations as possible not being a disease entity, is a condition probably highly prevalent in the population. We therefore wanted to investigate its prevalence and associated characteristics and to conduct a trial to explore the possible benefits of daily FOS-supplementation on BG stability in IRH. Primary aims:

1) To study the prevalence of IRH, in older Caucasian subjects who previously had participated in studies investigating the prevalence of undiagnosed hyperglycaemia, and through a case-control design explore its characteristics as compared with subjects with hyperglycaemic (T2DM or IGT) or normoglycaemic responses during an OGTT.

2) To evaluate, in a randomized crossover trial, the effect of FOS supplementation on reactive hyper- and hypoglycaemia, lipids and anthropometric parameters.

2. METHODS

This study, that was conducted at the Asker and Baerum Hospital, a secondary referral hospital in Southern Norway serving a population of approximately 150000, investigated the prevalence of IRH in subjects without a previous diagnose of diabetes or pre-diabetes, and compared anthropometric measurements, blood sample measurements, medication use, and cardiovascular (CV) complications and CV risk factors in subjects with type 2 DM (T2DM), impaired glucose tolerance (IGT) or those being normoglycaemic (NGT). This was done by a pooled analysis of the databases from two case-control studies; the Asker and Baerum Atrial Fibrillation study (n=152) (97) and the Glucose ABnormalities in Ischemic conditions study (n=210) (98). In short, these studies showed a high prevalence of undiagnosed abnormal glucose metabolism (> 50%) in patients with either long-standing atrial fibrillation (≥ 5 years) or CV complication, irrespective of vascular bed involved.

In addition, through an exploratory pilot trial (ClinicalTrial Gov. Id.: NCT00802971) we assessed the impact of oligofructose on reactive hypoglycaemia and parameters of glucometabolism in subjects with IRH, recruited from the two cohorts above, in a randomized, 4 weeks, crossover, pilot trial (FOS study). The protocol was approved by the Regional Committee for Medical Research Ethics, Norway and by the Norwegian Data Inspectorate. Each subject gave informed written consent before participating in the study that was conducted according to the Helsinki declaration. No compensation was given.

2.1 Classification of dysglycaemia, definition of IRH and assessment of glucometabolic parameters

An OGTT with ingestion of 75g glucose dissolved in 300ml water flavoured with citric acid was performed according to WHO standards, but with the supplement of a 1hour (h)-glucose measurement in all study participators. Blood glucose during the OGTT was analyzed immediately in capillary whole blood (photometer; HemoCue, Ängelholm, Sweden). The OGTT results were classified as 1) IRH if 1h- or 2h- glucose levels ≤ 3.9 mmol/L or if 1h- or 2h- glucose levels were < fasting glucose (fBG) (and no evidence of T2DM or IGT), 2) T2DM (fBG ≥ 6.1 mmol/L or 2h BG ≥ 11.1 mmol/L), 3) IGT (fBG < 6.1 mmol/L and 2h BG [7.8 – 11.1) mmol/L) or 4) NGT (fBG < 6.1 mmol/L and 2h BG < 7.8 mmol/L). The three latter was classified according to criteria of the World Health Organization (WHO) (117).

Insulin was analyzed by radioimmunoassay using an antibody with no cross-reaction against pro-insulin (Diagnostic System Laboratories, Webster, TX). The homeostasis model

assessment for insulin resistance (HOMA-IR) was calculated in fasting conditions as plasma insulin (pmol/l) x blood glucose (mmol/L) / 135.

Glucagon was assessed by competitive radio immunoassay (Millipore Corporation, Billarica, Ma, US). HbA1c was analysed by colorimetric and immunoturbidimetrical methods in whole blood with an upper normal limit reference value of 6.1%. Serum levels of total cholesterol, high-density lipoprotein (HDL)-cholesterol, triglycerides (TG) and glucose were measured enzymatically, all using on a Cobas Integra 800 (Roche Diagnostics, Rotkreuz, Schweiz). Low-density lipoprotein (LDL)-cholesterol was calculated using Friedewald's formula.

Handling and analysis of the inflammatory parameters are previously described (97, 98).

2.2 FOS study – objectives

When screening for eligibility from the crossover intervention, all subjects with IGT or DM2 where excluded. Key variable was the registered hypoglycaemia during 2h OGTT as defined earlier.

Twelve subjects diagnosed with IRH who previously had participated in on of the two case-control studies, were recruited by written invitation to participate in a four-week, parallel-group, crossover, open randomized intervention study comparing no treatment vs. fructo-oligosaccharide (F.O.S., BioCare Ltd. Birmingham, Great Britain) supplement. Patients were only included if they fulfilled the above IRH criterions but were excluded in the case of liver disease, insulinoma, gastrointestinal disease history, previously bariatric surgery or having the potential to become pregnant.

Primary objective was to evaluate FOS' effect on reactive hypo- and hyperglycaemia associated with IRH assessed by a 4-h OGTT. Secondary objectives were to evaluate impact of FOS on lipids, glucometabolic and anthropometric values and change in the 24h interstitial glucose AUC assessed by CGSM.

2.3 Crossover study details

Baseline procedures included fasting blood sampling and analysis (fasting blood glucose, HbA1c, lipids, HDL- and LDL-cholesterol, total cholesterol, triacylglycerol, insulin, glucagon, creatinine, CRP), measurement of anthropometric measures (weight and height), resting supine blood pressure (Omron, M6 Comfort, Omron Healthcare Co., Ltd. Kyoto, Japan) and questionnaires (intake of dietary fiber, frequency of meals, evidence of symptoms or signs of hypoglycemic episodes, use of

medication, leisure time physical activity and smoking, Appendix c).

In the first two weeks of the study, half of the participators were randomized to twice-daily FOS supplementation (2 x 10g) provided as powder in sealed bags to be dissolved in tap water and drunk within 20 minutes prior to breakfast and dinner. The resting half received no treatment. At day 12, all participators were advised to follow a written, pre-defined, food plan for 40 hours (1800 kcal/24 h for women and 2200 kcal/24 h for men, Appendix A and B, respectively). At day 13, all participators came to the hospital for registration with CGMS (CGMS Minimed®, CA, US or Medtronic Guardian RT Minimed, CA, US) to be used for 24 hours. At day 14 the participators came, in fasting state, to the hospital between 8 – 10a.m. for venous blood sampling (haemology, lipids and hormones), a 4h OGTT and detachment of the CGMS system. The following two weeks, these assessments were repeated for both groups, but then respectively without, and with, twice-daily FOS supplementation (crossover study).

All participators received a glucose meter (Freestyle Lite, Abbott) for capillary blood glucose measurements and a diary for reporting hypoglycemic symptoms (e.g. nausea, tremor, coldness, hunger, aggressiveness, or headaches) during the duration of the study. All participators also performed a 7-point blood glucose (at 8a.m., 10a.m., 12p.m., 14p.m., 17p.m., 830p.m., 1130p.m.) profile during the period of the CGMS registrations. During the 4-week period, subjects were also asked to grade any hypoglycaemic symptoms from the least to the most bothersome (0-10). Adverse events, whether related to fiber or not (e.g. abdominal pain, eructation, distension, borborygmi, flatulence, bloating, and diarrhea) were registered in the same diary.

2.4 Statistical analysis and sample size calculation

Sample size calculation for the exploratory pilot trial where based on a study in 13 subjects with T2DM where 24h plasma glucose levels was reduced by 10% during fibre supplementation (100). Hence we expected that 50% of participators with IRH receiving FOS would experience a blood glucose stabilizing effect as defined by no longer fulfilling 2h OGTT IRH definition as compared to 10% among those not receiving FOS. Our null hypothesis was that there should be no difference with regards to the impact of FOS on these criteria, and as we wanted a statistical power of 80% and an alpha error level of 5%, we needed 15 individuals in total. To account for drop-out we therefore decided to include 16 subjects.

Data analysis was performed using SPSS statistical software version 17.0.1 for Windows (SPSS Inc., Illinois, US). Results for continuous variables are presented as means and respective standard deviations as well as minimum and maximum values, unless otherwise stated. Between-

group statistical analysis of continuous parameters was examined for statistical significance with student's t-test for two independent samples in the case control study and in the randomised crossover trial the two pairs of continuous parameters were assessed with paired students t-test (normal distributed data) or Wilcoxon Signed Ranks test (non-normal distribution). Correlation coefficients are univariate derived using Spearman's correlation. Categorical variables are presented as counts or proportions (%) and statistical comparisons of these parameters were carried out by chi-squared test or the Fischer exact test (where $n < 5$).

3. RESULTS

3.1 Prevalence of IRH

The ABAF and GABI study population consisted of a total of 362 subjects (146 females [40.3%]), aged 45 – 87 (mean ± SD 71 ± 9) years, all without previously known DM, of whom 215 (59.4%) had a prior CV complication (i.e. coronary artery disease, cerebrovascular disease or peripheral occlusive arterial disease) and 30 (19.5%) atrial fibrillation.

All subjects performed a capillary 2h OGTT with the ingestion of 75g glucose, according to WHO standards. The OGTT revealed that 42 (11.6 %) of the subjects had undiagnosed type 2 DM (T2DM) (fasting capillary blood glucose [fcBG] ≥ 6.1 mmol/L or 2h-cBG ≥ 11.1 mmol/L), whereas a non-diabetic hyperglycaemic reactive response was found in 71 (19.6 %), i.e. impaired glucose tolerance (IGT [fcBG concentration < 6.1 and 2h-cBG 7.8 - 11.0 mmol/L]) and a hypoglycaemic reactive response, defined by IRH (fcBG ≤ 3.9 or 1h- or 2h-cBG < cfBG [T2DM and IGT excluded]) in 45 (12.4 %). 204 subjects (56.4%) were considered NGT, although 68 (18.8 %) of these had impaired fasting glycaemia (IFG) (fcBG 5.6 - 6.1 mmol/L and a 2h-cBG < 7.8 mmol/L). However, in the further analysis the IFG group is considered as, and comprised amongst the NGT group, since these subjects are lacking a pathological reactive glucose response. Figure 4 indicates the mean glucose values for the different groups.

3.2 Characteristics of IRH

Characteristics according to glucometabolic classifications (T2DM, IGT, IRH, NGT) are given in Table 2. Subjects in the IRH group (68 ± 10 years) was significantly younger than those in the T2DM (73 ± 7 years, p = 0.02) and IGT group (74 ± 6 years, p < 0.001), but not as compared to the NGT group (70 ± 9 years, p = 0.06). No between-group difference was seen in BMI or waist- or hip circumference. Overall, there was a significant positive correlation between BMI, weight, waist circumference and hip circumference with cfBG and 1h-cBG (Table 3), which also tended to be the case within each separate group (data not shown).

Of note was also that the subjects in the IRH group had a lower CAD prevalence vs. the other groups, i.e. amongst l1.1% of IRH subjects whereas 23.5% in the NGT group (p=0.06), 32.4% in the IGT group (p=0.008) and 33.3% in the T2DM group (p=0.009). Correspondingly, also, the use of CV drugs (i.e. beta blockers, statins, warfarin, renin-angiotensin system blockers) was higher in all other groups (Table 2).

Glucometabolic and lipid parameters

HbA1c, fasting plasma glucose, insulin and HOMA-IR were significantly lower in the IRH group as compared to the T2DM group (Table 4). This was true for the 1h- and 2h-cBG values as compared to the T2DM and IGT groups as well. As expected, overall HOMA-IR correlated significantly positive with fcBG, 1h- and 2h- BG levels, indicated in Table 3. This was also the case when each group was analysed separately, although level of significance was not always met (data not shown).

Lipid values (except TG) were lowest in the T2DM group (Table 4), whom also had the highest proportion of statin users (Table 2). However, no differences in lipid values were noted for IRH vs. the other groups, despite also here a difference in the proportion of statin treated subjects (Table 2).

Parameters of inflammation and the IGF system axis

Inflammatory- and IGF system axis parameters evaluated indicated a more favourable profile in the IRH subjects for most parameters. Statistical significance was however only reached against the T2DM group (for IL-10, TNFR-1, TGFB-1, IGF-1 and CRP) and in the IGT group (for TNFR-1, IGF-1 and CRP) (Table 4).

In a bivariate overall correlation of these parameters vs. cfBG, 1h- and 2h-cBG, there were seen a significant relation against white blood cells, CRP and TNFR-1, and a significant correlation between IGFB-3 and IGF-1 and 2h-cBG (Table 3).

3.3 Impact on parameters of glycaemia and lipids by dietary supplementation of fructose oligosaccharide (FOS).

Baseline characteristics

The randomized trial took place between December 2008 and March 2009. Six men and six women (mean age 56 $\pm$ 8 years, BMI 25.0 $\pm$ 2.9 kg/m2, HbA1c 5.8 $\pm$ 0.3%) were recruited from the IRH group (with mean OGTT results: cfBG, 1h- and 2h-BG of respectively 5.3 + 0.5, 8.4 + 2.2 and 4.4 $\pm$ 0.9 mmol/L) as previously described, by written invitation, to participate in a 4-week crossover study. Amongst these 12 subjects, two (17%) reported daily symptoms indicating hypoglycaemia, while a total of seven (58%) reported to experience sporadic symptoms of hypoglycaemia in daily life.

In agree with the protocol, the study consisted of two consecutive two-week sequences i.e. with and without FOS supplementation administrated twice daily (2 x 10g) taken breakfast and dinner.

According to self-reported inquires, the participants consumed a mean number of five daily meals and 2.5 $\pm$ 1.1 of those meals contained fibrous ingredients (defined as lentils, oatmeal or nuts, whole kernel bread, vegetables or fruit).

Leisure time physical activity was reported to 5.8 $\pm$ 2.4 hours. 10 (83%) of the participants accentuated a healthy diet, in conjunction with the baseline propitious characteristics in Table 5 and 6 (normotensive, normal weight, one current smoker, laboratory parameters within reference values).

Treatment sequence results

Eight of the 12 participants were randomly (randomization list generated by computer program [randomizer.org]) assigned, using sealed envelope kept away from personnel involved in the study, to receive FOS supplementation for the initial 2-week sequence. For all 12 subjects, mean days with FOS consumption were 16 $\pm$ 4.5. There were no dropouts.

4h OGTT

At the end of each 2-week sequence a 4h OGTT was conducted with cBG measures every 30 minutes. In the preceding 36 hours of the OGTT all subjects followed a standardized diet of 1800 kcal for women and 2100 kcal for men, with a fibre content of 31 and 40g, Appendix a and b, respectively. The dietary compliance in these two diet-controlled days was excellent as assessed by direct question.

The results of the 4h OGTT are detailed in Table 7 and Figure 5 and 6 (a-l), the latter indicating individual OGTT data of FOS vs. no-FOS. As is evident, the definite effect of FOS is assessed by modulation of amplitude (zenith and nadir) and shape of the OGTT curve, where the shape index (a measure of glucose variation) improved non-significantly during FOS supplementation. All subjects had a biphasic OGTT shape curve with relatively high and early zeniths and slow and deeper nadirs (an indication of high glucose variability) before FOS supplementation, which was reduced to nine on FOS supplementation.

The blood glucose stabilizing effect was also noticed by a significant reduced glycaemic exposure (AUC) between 180 and 210 minutes in the FOS sequence (Table 7) and a lower

proportion of subjects with cBG measurements $\leq$ 3.9 mmol/L during the last 2 hours of the OGTT from 21 to 11 ($\chi^2 = 4.26$, $p = 0.04$, Figure 7).

CGMS test results and SMBG

CGMS registration was deemed successful if a set of 288 measurements/24h were available. Due to technical difficulties however, only four of the 12 CGMS-sets were valid. Notably, no participant finished premature due to sensor discomfort. Thus; since CGMS registrations were available for only 30% of participants, no meaningful analysis of this could be conducted.

However, study subjects were also asked to perform SMBG the preceding day of the 4h OGTT. These results are displayed in Table 8, indicating a tendency of a mediation of cBG in the forenoon hours.

Glucometabolic and anthropometric parameters

Table 9 shows the laboratory assessments following each intervention sequence. Wilcoxon signed-rank test gave significant reduction in glucose and total cholesterol following FOS sequence (5.4 $\pm$ 0.6 mmol/L vs. 5.1 $\pm$ 0.5 mmol/L, $p \leq 0.05$ and 5.3 $\pm$ 1.1 mmol/L vs. 4.9 $\pm$ 1.1 mmol/L, $p \leq 0.04$, respectively) and decrements in white blood cells, weight, insulin and insulin – glucagon ratio, notwithstanding they did not reach statistical significance.

3.4 Tolerability of FOS supplementation, FOS compliance and hypoglycaemic symptoms

All subjects enrolled in the present pilot intervention completed the study and ccompliance to FOS supplementation was high as assessed by direct questions. Any adverse events reported were of a mild to moderate nature and specific to GI discomfort (e.g. flatulence, abdominal distension and intestinal rumbling). One participant reported increased and prolonged satiety, another improvement in bowel function. The extent of hypoglycaemic symptoms announced did not diverse in the two intervention weeks.

The weight was stable throughout the 4 week period for all participants.

4. DISCUSSION

In this study, 10% of subjects in a relatively large and heterogeneous group of older adults reacted with a hypoglycaemic response during OGTT according to the proposed criterion of IRH, and two weeks diet supplementation with fibre (FOS) gave an overall more advantageous OGTT response (zenith, nadir and numbers of episodes of BG < 3.9 mmol/L levels), as well as had a beneficial impact on fasting total cholesterol and plasma glucose.

A prevalence of one in 10 subjects having a reactive hypoglycaemia is in line with studies from UK and US (101, 9), whereas others state this to be a rare phenomenon (32, 102). Interestingly, in lean, young women with PCOS, a reactive hypoglycaemia was seen in 50% (23).

Ever since Harris' (8) report of hypoglycaemic symptoms at BG values < 3.9 mmol/L, this defining limit has fluctuated (2, 3) making it troublesome to evaluate its true prevalence. In agreement with this, the abovementioned UK study set the hypoglycaemic threshold to 3.3 mmol/L yet Marks & Teale used 3.0 mmol/L (101, 9). Additionally, habitual glucose intervals changes according to age, as young, lean, healthy women with plasma glucose levels towards 2.2 mmol/L are not unusual (103) whereas in elderly people BG < 3.3 is an independent risk factor for in-hospital mortality (104). To emphasize this, our study population was pre-selected with a mean age of 72, with regard to 27 in Simpson's study of self applied participants.

As compared with those with hyperglycaemic reactive- or normoglycaemic responses, the IRH subjects were characterized of being younger, having less CV complications and a more favourable inflammatory- and glucometabolic profile, which also are previously described characteristics (23, 27). Contrary, the present study do not support a suggested higher prevalence of IRH in women (16) or in those with lower BMI (6, 21) which in our situation could colligate to selection bias.

Moderate elevated inflammatory parameters promote cardiovascular degeneration (105). Interestingly, when resemble the four groups together, we observed a lower proportion of CV complications in the IRH group, they also presented a more beneficial inflammatory and glucometabolic profile. Whether there is a link between these characteristics remain to be settled in further studies, but if this is the case it could be conflicting with studies showing that low blood glucose levels can heighten the level of inflammatory parameters (106). Insulin hypersensitivity and defects in gastrointestinal-pancreatic β-cell signalling network as has been reported in IRH (107) increase the occurrences of BG < 3.5 mmol/L in witch activates counterregulatory defences that will disturb everyday life with marked discomfort and attenuated intellectual or psychomotor function. Studies on driving performance also affirm disturbances in several neurological functions

at BG levels > 3 mmol/L (108). Moreover, bothersome clinical manifestations and clinical trivial events without biochemical hypoglycaemia might have impact on HRQoL (24) and theoretically, a low BG may increase food consumption or elaborate physical exercise in fear of symptoms.

The present investigation showed a beneficial effect of fibre in IRH. Apart from stabilizing glucose amplitude and reduce number of cBG measurements $\leq$ 3.9 mmol/L during the last 2 hours of the OGTT, also noticed was a significant flattened glycaemic exposure in the interval 180 – 210 minutes post glucose load and an improvement in shape index during FOS supplementation. Supported by the research of Yamashati et al. and Delzenne et al. (109, 110) we further observed a significant reduction in fasting plasma BG and total cholesterol, despite the fact that our study population was to a large extent healthy.

Test-meals containing FOS promotes a trend toward lower glycaemic responses and peak insulin levels (111). Although not significant, we observed beneficial adjustments in insulin and glucagon levels after 2 weeks of FOS intake comparable to the results of Jackson et al. and Kaur & Gupta, respectively (112, 113).

GIP and GLP-1 are major mediators in regulating postprandial insulin release and exhibit an insulin-like action on lipid metabolism (114, 115). In animal studies presenting the same glucometabolic modulations, these were attributed to the effects of inulin in increasing the secretion of GIP and GLP-1 from the caecum (116), and human studies affirm this observations (117) where incretins presumable are responsible for 70% of the insulin response during food intake in a healthy man (118). Also, FOS supplementation is linked to increased levels of pancreatic insulin content and to revert hepatic insulin resistance if the GLP-1 receptors are sufficiently functional in rats (116).

A significant decrement in fasting plasma glucose concentration proceeded the FOS sequence, supporting the findings of Yamashita et al., 1984 (109), Hidaka et al. (119), and Kok et al. (116) (the latter using rat-models). Luo et al., postulated this to relay on a decreased basal hepatic glucose production in relation to the short-chain fatty acid propionate (120) highlighted by the effect of long-term oral propionate in healthy subjects to decrease fasting serum glucose and maximum insulin increment during glucose tolerance testing (121).

Brun et al. (6) proposes that habitual activity level and diet may be important in the development of IRH. During moderate physical exercise glucagon and epinephrine are deficient and insulin secretion is stimulated, further amplify the risk of hypoglycaemia since frequent exercise increase insulin sensitivity. Taking this small sample size, their prominence to a healthy diet and high level of physical activity at baseline into consideration, the likelihood of modify glucometabolic parameters with fibre were expected to be limited. Furthermore were their habitual

numbers of daily meals reported to five, containing a high quantity of fibrous foodstuff, moreover decreasing the potential fibre effect of FOS.

All the subjects enrolled in the present pilot intervention were invited to participate, regardless of contributing symptoms to hypoglycaemia. The fact that our appending criteria was relatively wide, gave a heterogeneous study population difficult to collate with the results of other studies. 17% reported daily manifestations and 58% sporadic symptoms admitted to hypoglycaemia at enrolment and we could not find an ameliorating effect of FOS. This may relate to the short study duration and the low number of participants, but perhaps mostly the lack of apparent symptoms as a requisition in participating. We also noticed a skewed reporting of symptoms with a higher rate in the beginning of the intervention, in spite of FOS intake. Apart from supplementing two daily meals with FOS, the subjects were not given any other dietary or habitually instructions. This concern, beside the choice of patients, background diet (gastro intestinal microflora condition) and physical activity, should be taken in future investigations of FOS' ability in modulating glucose homeostasis. Besides, to accurately expose the relationship between low blood glucose and symptoms one should assess insulin and glucagon values throughout the OGTT, preferment using a hyperinsulinemic clamp.

FOS appears to have the potential of modulating glucose oscillations and ameliorate an impaired incretin effect, malfunctions commonly seen in diabetics. In T2DM, GLP-1 and GIP disturbances accompanies inappropriately regulated glucagon secretion that leads towards chronically hyperglycaemia and increased risk of micro- and macrovascular complications (122). Fructo-oligosaccharides also promotes satiety (123) and should therefore be considered to comprise a new nutritional approach in T1DM and T2DM patients.

This pilot study was of short duration and only included twelve participants without clinical post-study manifestation of symptoms, thereupon prone to selection biases. Although randomized, it was not double-blind and only enclosed one study centre. Due to shortcoming in time, we excluded a wash-out period between the treatment sequences, illustrating the possibility of FOS having a prolonged effect in the no-treatment weeks. Gibson et al. reported that for the population of bifidogenic bacteria to return to pre-supplementation numbers was determined by the dosage, with 1 day being necessary for each gram of inulin used per day (89)

Although the benefits of fibre intake are unequivocal, current recommendations of intake and actual consumption disagree with 50% in the American population (124) as well as in the Norwegian (83). We recognize the potential of FOS supplementation in increasing these values.

5. CONCLUSION

A reactive hypoglycaemic response following ingestion of glucose during an OGTT is prevalent and such a response could be modulated by dietary supplementation of fibre. Such a benefit is also likely in general life, in particular for those with sub-optimal fibre consumption and for those that reports some kind of hypoglycaemic symptoms. Because the intake of dietary fibre is significantly lower than the recommended amount for the population, the addition of oligofructose to a regular diet will benefit consumers by increasing overall fibre intake; and due to its unique composition generating higher viscosity than most polysaccharides, this functional fibre can also provide consumers added physiological benefits including, but not limited to increased glycaemic stability and LDL cholesterol.

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7. TABLES

Table 1. List of conditions associated with hypoglycaemia in adults without diabetes mellitus according to a healthy or ill appearance (modified from Harris, 1920 and Gama et al., 2003) (4, 147).

Healthy appearing patient	*Ill appearing patient*
Endogenous hyperinsulinism (insulinoma) (20) and autoimmune insulin syndrome (125)	Hepatic or cardiac failure, sepsis (138)
Functional β-cell disorders (nesidioblastosis) (126)	Renal failure and concomitant use of trimetoprim (139) or quinidine (140)
Non-islet cell tumour (127)	Inborn error of metabolism, i.e. Type I Glycogen storage disease (141)
Noninsulinoma pancreatogenous hypoglycaemia syndrome (reduced glucagon and cortisol, growth hormone and/or epinephrine) (128, 37, 129);	Congenital hypopituitarism (142) , growth hormone (143) or corticotrophin (144); deficiency
Post gastric bypass hypoglycaemia (130)	Addison's disease (129)
Intense exercise (131) Ethanol (132)	Galactosemia (145) or fructose-1,6-diphosphatase deficiency (146)
Undernutrition (133)	
Drugs (insulin or insulin secretagogue, sulphonylureas (134), salicylates (135), quinine (136), haloperidol (137), β-adrenergic blocking agents (134)	

Table 2. Characteristics of subjects (n =362) in a case-control study according to glucometabolic classification.

	IRH	T2DM	IGT	NGT
n	45 (12.4%)	42 (11.6%)	71 (19.6%)	204 (56.4%)
Anthropometric measurements				
Gender (F/M)	8 (17%)/38 (83%)	12 (29%)/30 (71%)	34 (48%)/37 (52%)	92(45%)/112 (55%)
Age (years) (mean + SD)	68 ± 10	73 ± 7*	74 ± 6***	70 ± 9
BMI (kg/m^2) (mean + SD)	24.7 ± 3.3	25.3 ± 3.8	25.3 ± 3.7	25.0 ± 3.5
Waist circ. (cm) (mean + SD)	92 ± 10	94 ± 12	92 ± 13	90 ± 11
Hip circ. (cm) (mean + SD)	101 ± 6	102 ± 8	101 ± 8	101 ± 9
Cardiovascular complications n (%)				
CAD	5 (11.1%)	14 (33.3%)**	23 (32.4%)**	48 (23.5%)§
CVD	4 (8.9)	3 (7.1)	12 (16.9)	11 (5.4)
Concomittant medications n (%)				
Betablockers	5 (11.1)	17 (40.8)***	23 (32.4)**	60 (29.4)**
RASB	5 (11.1)	7 (16.7)	10 (14.1)	16 (7.8)
Aspirin	17 (37.8)	20 (47.6)	26 (36.6)	59 (28.9)
Warfarin	1 (2.2)	11 (26.2)***	7 (9.9)	10 (4.9)
Statins	14 (31.1)	29 (69.0)***	36 (50.7)*	73 (35.8)

, **, *: Significant at the 0.05, 0.01, 0.001 level respectively vs. IRH-group, §: p=0.06.*

BMI: body mass index, CAD: coronary artery disease, CVD: cerebrovascular disease, RASB: renin-angiotensin system blockers

Table 3. Overall (n=362 or n=208) bivariate correlation (Pearsons r) between anthropometric, and HOMA-IR or fasting parameters of the inflammatory and IGF-system and glucose parameters of the OGTT. (r-values and level of significance indicated).

	fcBG	1h-cBG	2h-cBG
BMI (kg/m^2)	0.212***	0.167**	0.001
Body weight (kg)	0.226***	0.171***	-0.052
Waist circum. (cm)	0.230***	0.206***	0.028
Hip circum. (cm)	0.161**	0.126*	0.040
HOMA-IR	0.348***	0.232***	0.156**
White blood cells (10^9/L)	0.144**	0.189***	0.122*
CRP (mg/L)§	0.172**	0.173**	0.274***
IL-10 (pg/mL)	-0.096	-0.079	-0.049
TGFB-1 (ng/mL)	-0.101	-0.090	-0.125¤
TNFR-1(pg/mL)§	0.152*	0.160*	0.269***
IGFBP-1(µg/mL)§	-0.102	-0.050	0.096
IGFBP-3(µg/mL)§	-0.034	-0.083	-0.162*
IGF-1(ng/mL)§	0.057	0.003	-0.204**

§: n = 208. For all other values n = 362.

, **, *: Significant at the 0.05, 0.01, 0.001 level. ¤ Border line significant (p = 0.07).*

fcBG: fasting capillary blood glucose, BMI: body mass index, HOMA-IR: homeostasis model assessment of insulin resistance, CRP: c-reactive protein, IL-10: interleukin 10, TGFB-1: transforming growth factor β1, TNFR-1: tumour necrosis factor-receptor, IGFBP-1: insulin-like growth factor binding protein, IGF-1: insulin-like growth factor.

Table 4. Characteristics of the GABI and ABAF study population according to glycometabolic classification. (Mean ± SD).

	IRH (N=45)	T2DM (N=42)	IGT (N=71)	NGT (N=204)
Fasting glycaemic parameters				
HbA1c (%)	5.7 ± 0.4	6.0 + 0.6**	5.9 ± 0.4	5.7 + 0.4
fpBG (mmol/L)	5.2 ± 0.5	6.2 ± 0.9***	5.4 ± 0.5*	5.1 ± 0.5
Insulin (pmol/L)	81.0 ± 32.8	113.8 ± 77.8*	100.0 ± 60.6	90.6 ± 3.5
HOMA-IR	3.5 ± 1.5	6.2 ± 4.5***	4.6 ± 2.9*	4.0 ± 2.2
2h OGTT results				
fcBG (mmol/L)	5.3 ± 0.5	6.3 ± 0.8***	5.4 ± 0.5	5.2 + 0.4*
1-h cBG (mmol/L)	8.4 ± 2.2	12.9 ± 2.4***	10.7 ± 1.8***	8.7 + 1.8
2-h cBG (mmol/L)	4.4 ± 0.9	10.8 ± 3.2***	8.8 ± 0.8***	6.5 + 0.7***
Lipid parameters				
TG (mmol/L)	1.0 ± 0.5	1.4 ± 0.8*	1.3 ± 0.9	1.2 ± 0.7
Tot. chol. (mmol/L)	5.2 ± 1.0	4.7 ± 1.0*	5.2 ± 1.3	5.3 ± 1.1
HDL (mmol/L)	1.6 ± 0.4	1.5 ± 0.6	1.7 ± 0.5	1.7 ± 0.5
LDL (mmol/L)	3.1 ± 0.9	2.5 ± 0.9**	3.0 ± 1.1	3.1 ± 1.0
Parameters of inflammation and the IGF-system				
White blood cells (10^9/L)	6.5 ± 1.6	6.8 ± 2.1	6.8 ± 1.8	6.2 ± 1.6
IL-10 (pg/mL)	0.6 ± 0.1	1.1 ± 1.2*	0.7 ± 0.4	1.8 ± 6.5
CRP (mg/L)	2.3 ± 2.7	5.6 ± 6.6*	4.6 ± 5.2*	3.1 ± 4.2
TNFR-1 (pg/mL)	779.2 ± 200.4	1196.6 ± 675.9**	1014.1 ± 421.4**	908.9 ± 355.2
IGFBP-1 (µg/mL)	44.9 ± 30.0	50.5 ± 42.0	47.4 ± 36.5	50.7 ± 37.0
IGFBP-3 (µg/mL)	1.7 ± 0.4	1.5 ± 0.5	1.5 ± 0.4	1.5 ± 0.4
TGFB-1 (ng/mL)	7.5 ± 4.4	5.3 ± 2.1*	6.4 ± 3.4	6.7 ± 3.6
IGF-1 (ng/mL)	80.9 ± 22.4	64.6 ± 26.2*	67.2 ± 25.8*	71.8 ± 29.3

, **, *: Significant at the 0.05, 0.01, 0.001 level respectively vs. IRH-group.*

HbA1c: Glycosylated haemoglobin A1c, fpBG: fasting plasma blood glucose, HOMA-IR: homeostasis model of inulin resistance, fcBG: fasting capillary blood glucose, TG: triglycerides Tot. chol.: total cholesterol, HDL/LDL: high/low density lipoprotein, IL-10: interleukin 10, CRP: c-reactive protein, TNFR-1: tumour necrosis factor-receptor 1 IGFBP: insulin-like growth factor binding protein, TGFB-1: transforming growth factor β1, IGF-1: insulin-like growth factor.

Table 5. General characteristics and observations of IRH study participants at baseline.

	Mean ± SD	Min - max
Age (years)	56.3 ± 8.3	41 – 75
Weight (kg)	76.5	54.9 – 95.5
BMI (kg/m^2)	25.0 ± 2.9	20.0 – 29.1
Systolic blood pressure (mmHg)	123.1 ± 21.7	90.5 – 167.5
Diastolic blood pressure (mmHg)	78.5 ± 12.7	63.5 – 103.0
Number of meals	4.7 ± 0.9	3 – 6
Leisure time physical activity (min/week)*	347.1 ± 144.5	70 – 540
Nr. of daily meals containing fibre**	2.5 + 1.1	1 – 4
TV/reading (min/week)	1440.0 ± 968.1	525 – 4200
Smokers (n (%))	1 (8.3)	
Coronary artery disease (n (%))	2 (16.7)	
Cerebrovascular disease (n (%))	1 (8.3)	
Beta blocker (n (%))	1 (8.3)	
Angiotensin receptor blocker (n (%))	2 (16.7)	
Aspirin (n (%))	3 (25)	
Warfarin (n)	0	
Statin (n (%))	3 (25)	

**All participants performed ≥ 4 work out sessions/week*
*** Selected fibre containing groceries accessed by questionnaire*
BMI: body mass index

Table 6. Laboratory parameters of IRH study participants at baseline (fasting).

	Total	Range
Leukocytes (10^9/L)	5.1 ± 0.8	3.9 – 6.7
CRP (mg/L)	1.0 ± 0.9	0.3 – 3.4
ASAT (U/L)	25.6 ± 6.7	18 – 40
ALAT (U/L)	25.3 ± 14.7	4 – 57
Cholesterol (mmol/L)	5.3 ± 1.1	3.6 – 7.2
TG (mmol/L)	1.0 ± 0.5	0.4 – 2.2
HDL (mmol/L)	1.8 ± 0.6	1.0 – 2.9
LDL (mmol/L)	3.0 ± 0.9	1.6 – 4.1
Glucose (mmol/L)	5.4 ± 0.6	4.4 – 6.1
HbA1c (%)	5.8 ± 0.3	5.4 – 6.5
Insulin (pmol/L)	26.7 ± 15.7	15 – 72
Glucagon (pmol/L)	17.6 ± 3.6	11.4 – 22.3
Insulin/Glucagon ratio	1.4 ± 0.8	0.9 – 3.5
HOMA-IR*	1.0 ± 0.7	0.6 – 2.9

CRP: c-reactive protein, ASAT: aspartate aminotransferase, ALAT: alanine amino transferase, TG: triglycerides, HDL: high density lipoprotein, LDL: low density lipoprotein, HbA1c: Glycosylated haemoglobin A1c, HOMA-IR: homeostasis model of inulin resistance.

$* \frac{[\text{fasting plasma insulin}]\,[\text{fasting plasma glucose}]}{135}$

Table 7. Sequence-end results for the 4h-OGTT of each 2-week cycle. (Mean values indicated).

	Sequence A (FOS) n =12	Sequence B (No FOS) n = 12	Statistical analysis (mean diff/t-value/p-value)
Glucose levels			
Fasting glucose (mmol/L)	5.2 (0.4)	5.5 (0.6)	-0.3/-1.6/0.15
Glu_30 min (mmol/L) (SD)	10.3 (2.0)	10.5 (1.8)	-0.2/-0.3/0.77
Glu_60 min (mmol/L) (SD)	9.3 (2.1)	10.2 (2.3)	-0.9/-1.3/0.24
Glu_90 min (mmol/L) (SD)	7.2 (1.7)	7.9 (1.7)	-0.7/-1.3/0.20
Glu_120 min (mmol/L) (SD)	5.7 (1.8)	5.8 (1.7)	-0.05/-0.09/0.93
Glu_150 min (mmol/L) (SD)	4.5 (1.4)	4.7 (1.3)	-0.2/-0.7/0.48
Glu_180 min (mmol/L) (SD)	4.4 (0.6)	4.0 (0.8)	0.4/2.6/0.03
Glu_210 min (mmol/L) (SD)	4.4 (0.3)	4.1 (0.3)	0.3/2.0/0.07
Glu_240 min (mmol/L) (SD)	4.5 (0.3)	4.4 (0.4)	0.2/0.8/0.43
AUC			p-value
0-30 (mmol/L·min)	233 (32.4)	240 (32.3)	0.56
30-60 (mmol/L·min)	295 (50.7)	310 (58.5)	0.39
60-90 (mmol/L·min)	248 (53.2)	271 (52.9)	0.21
90-120 (mmol/L·min)	194 (46.2)	205 (43.3)	0.39
120-150 (mmol/L·min)	153 (42.5)	157 (40.9)	0.72
150-180 (mmol/L·min)	133 (28.7)	130 (29.9)	0.48
180-210 (mmol/L·min)	132 (9.9)	121 (16.1)	0.02
210-240 (mmol/L·min)	135 (7.0)	128 (9.4)	0.11
Total (mmol/L·min)	1522 (62.2)	1561.3 (72.5)	0.28
Parameters of the OGTT curve			p-value
Shape-index*	1.5 (1.6)	2.1 (1.7)	0.35
Shape of the OGTT curve			Chi-Squared test p-value
monophasic	3	0	0.08
biphasic	9	12	0.5
cBG counts $\leq$ 3.9 mmol/L	11	21	0.04

**Glu_90 min – Glu_120 min*
AUC: area under curve

Table 8. Sequence-end results for self monitoring of blood glucose. (Mean values indicated).

Mean values (SD)	Sequence A (FOS) n = 12	Sequence B (no FOS) n = 12	Statistical analysis (mean diff./t-value/p-value)
8a.m. (mmol/L (SD))	5.3 (0.4)	5.7 (1.2)	-0.4/-1.3/0.22
10a.m. (mmol/L (SD))	5.3 (0.8)	6.4 (2.1)	-1.1/-1.2/0.31
12a.m. (mmol/L (SD))	5.8 (1.6)	6.8 (1.7)	-1.0/-1.0/0.34
2a.m. (mmol/L (SD))	5.9 (1.2)	5.4 (1.0)	0.6/0.6/0.58
5a.m. (mmol/L (SD))	5.4 (1.0)	6.1 (1.5)	-0.7/-1.3/0.23
7.30p.m. (mmol/L (SD))	6.2 (1.2)	5.1 (0.9)	1.2/2.3/0.05
10.30p.m. (mmol/L (SD))	6.4 (1.2)	6.1 (0.4)	0.3/0.8/0.44
AUC_glucose (mmol/L·min)	84.1 (3.4)	85.4 (2.2)	p = 0.75

AUC: area under curve

Table 9. Sequence-end results of fasting glucometabolic parameters and anthropometric measures of each 2-week cycle. (Mean values (SD)).

	Sequence A (FOS) n = 12	Sequence B (no FOS) n = 12	Statistical analysis (mean diff./p-value)
HbA1c (%)	5.9 (0.2)	5.9 (0.2)	-0.5/0.59
Glucose (mmol/L)	5.1 (0.5)	5.4 (0.6)	-2.0/0.05
Insulin (pmol/L)	23.8 (10.8)	25.1 (11.8)	-0.9/0.35
Glucagon (pmol/L)	17.0 (4.4)	16.6 (3.4)	-0.36/0.72
HOMA-IR (%)	1.0 (0.5)	1.2 (0.7)	-1.4/0.16
Insulin-Glucagon ratio	1.4 (0.6)	1.5 (0.6)	-0.7/0.48
Total cholesterol (mmol/l)	4.9 (1.1)	5.3 (1.1)	-0.2/0.04
LDL cholesterol (mmol/l)	2.7 (0.7)	3.0 (0.9)	-1.1/0.25
HDL cholesterol (mmol/l)	1.7 (0.6)	1.9 (0.7)	-2.6/0.01
Triglycerides (mmol/l)	1.0 (0.4)	1.0 (0.7)	-1.0/0.31
CRP (mg/L)	1.6 (1.7)	0.9 (0.9)	-2.0/0.04
White blood cells (10^9/L)	4.8 (1.1)	5.1 (1.1)	-0.9/0.35

Abbreviations: BP – blood pressure, HOMA-IR: homeostasis model of inulin resistance
HDL: high density lipoprotein, LDL: low density lipoprotein. ARB: angiotensin receptor blocker

8. FIGURES

Figure 1. Venous blood glycaemic thresholds for secretion of counterregulatory hormones and onset of physiological, symptomatic and cognitive changes in response to hypoglycaemia in non-diabetic humans (Reproduced from Hypoglycaemia in Clinical Diabetes, Frier and Fisher (Eds) 2nd ed. 2007 with permission from John Wiley and Sons, UK).

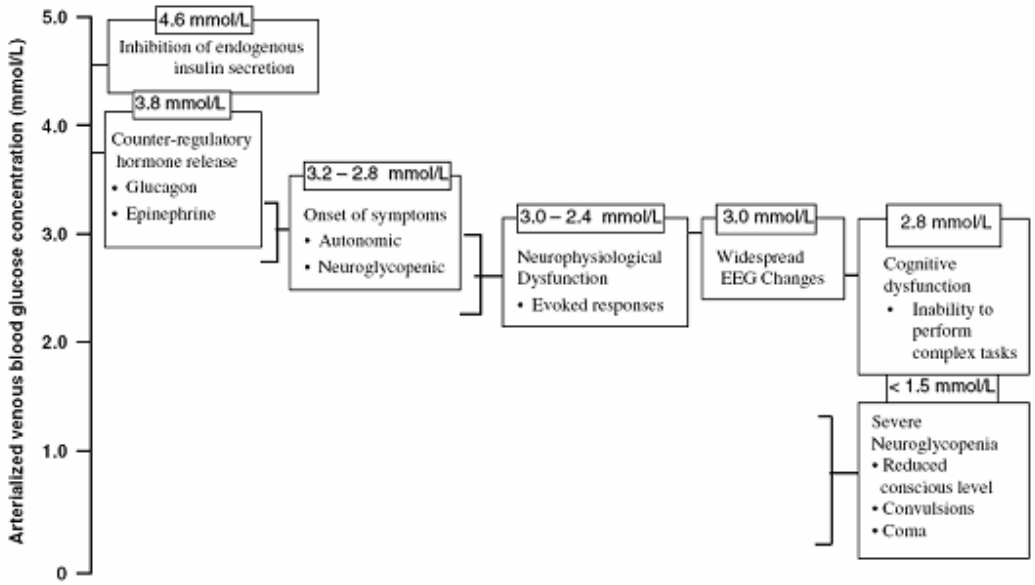


Figure 2. Mono- and biphasic (thin line) pattern of the OGTT curve.

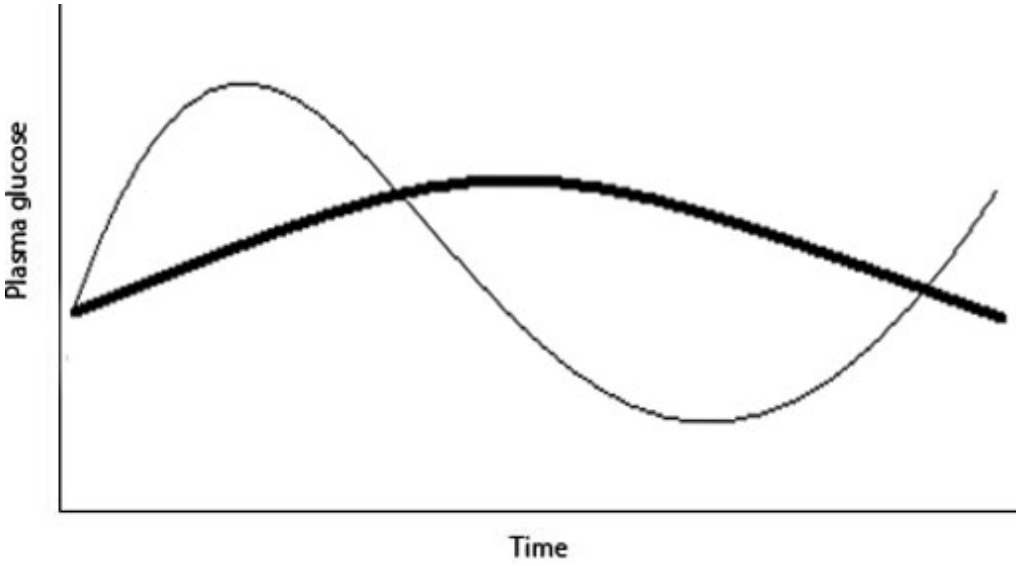


Figure 3. Chemical structure of fructo-oligosaccharide (n = 2 – 4 fructose residues).

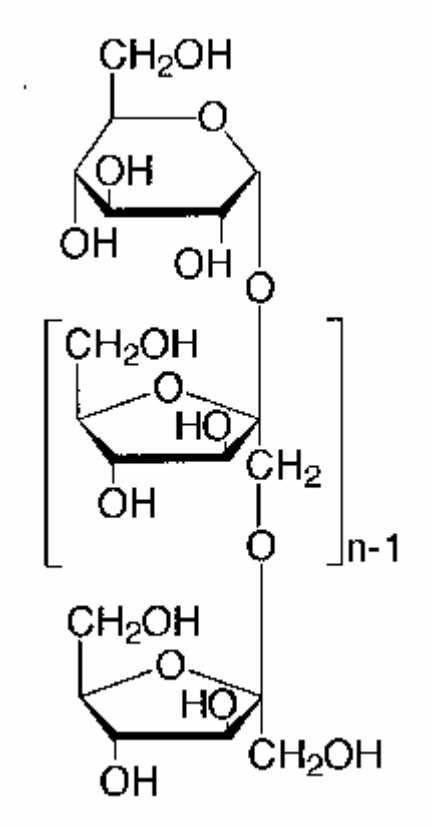
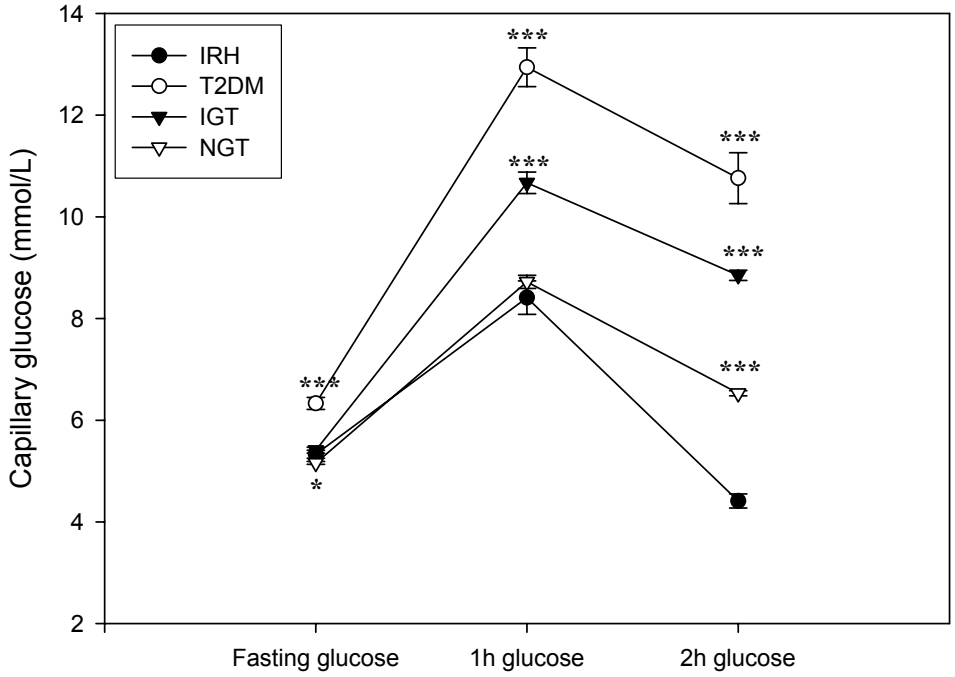
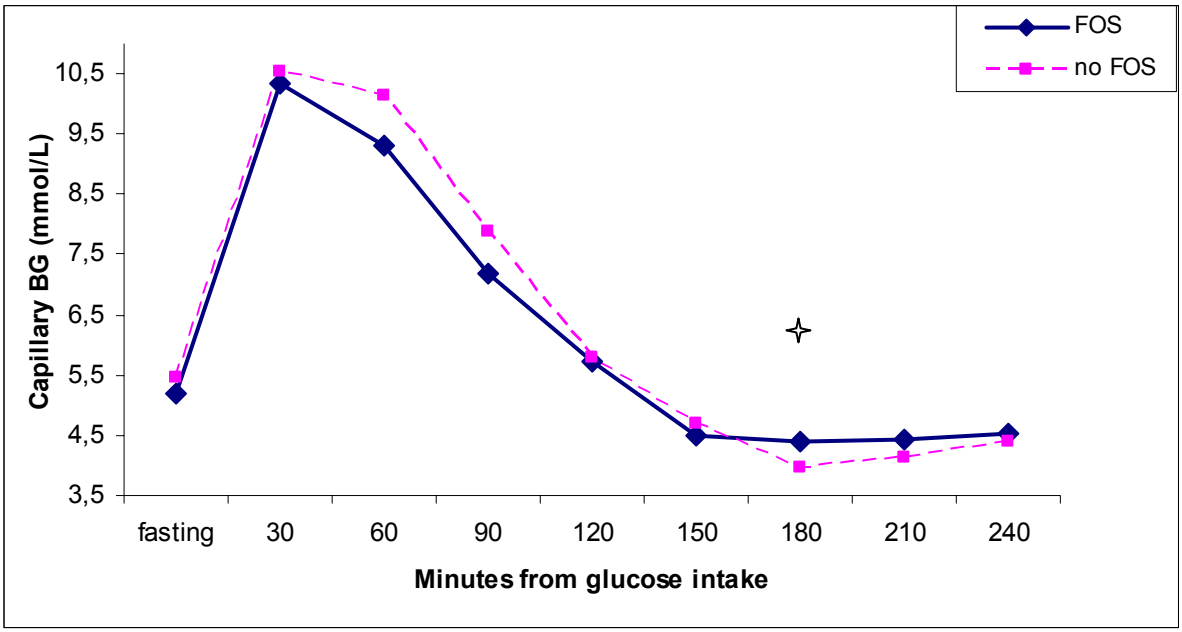


Figure 4. Glucose levels during an OGTT in the different glucometabolic groups (mean ± SD).



*,***: $p < 0.05$, 0.001 vs. IRH

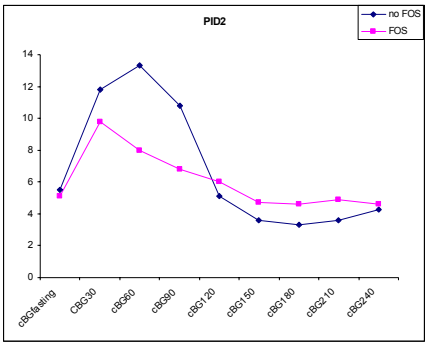
Figure 5. Sequence-end mean cBG values of the 4h-OGTT in each 2-week cycle.



✧: $p \leq 0.05$

Figure 6(a-l). Individual 4h OGTT glycaemic profiles in each 2-weeks intervention sequence.

a)



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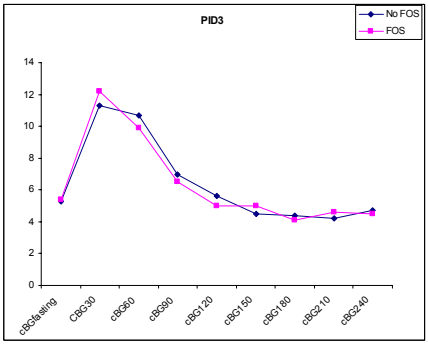

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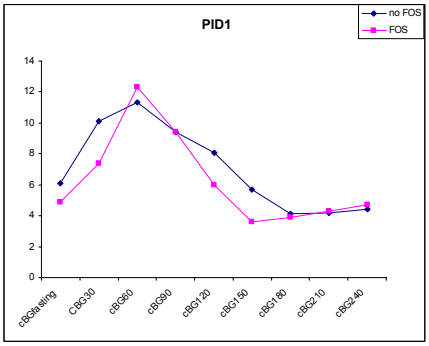

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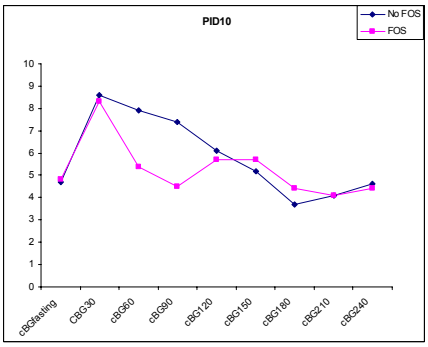

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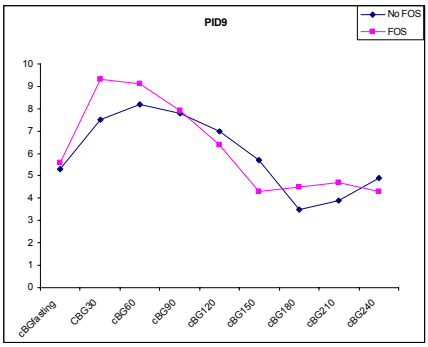

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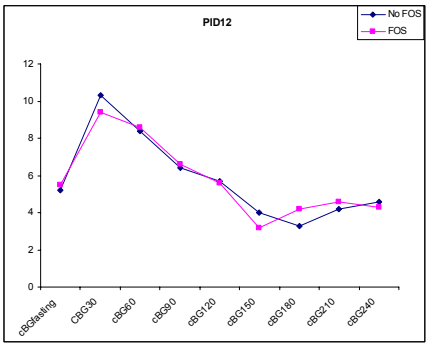
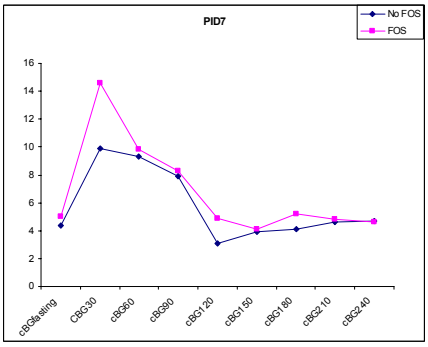
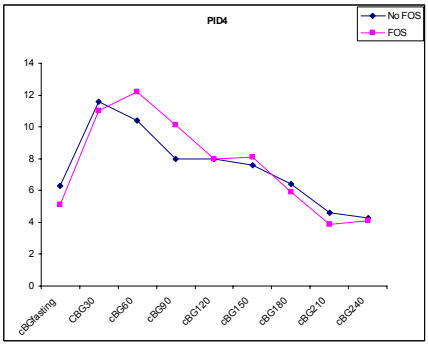


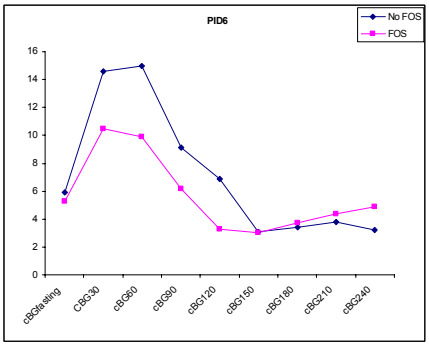
g)



h)



i)



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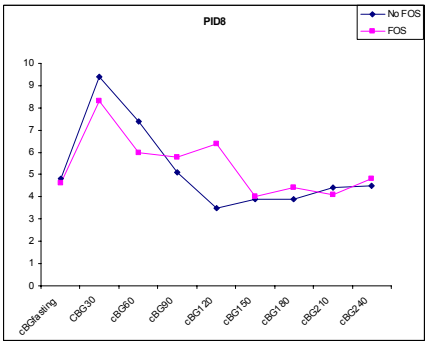

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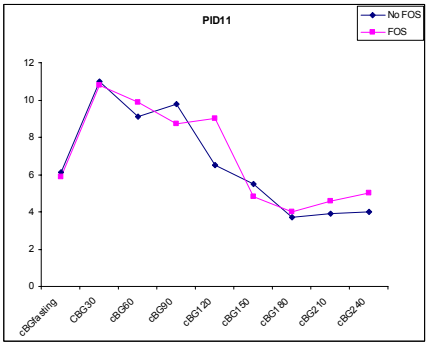

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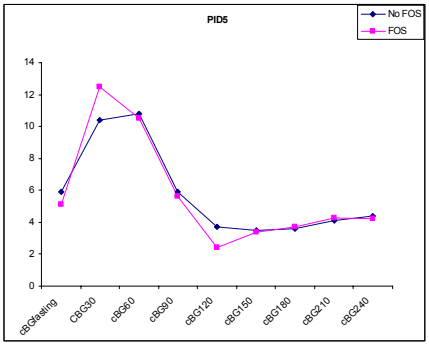
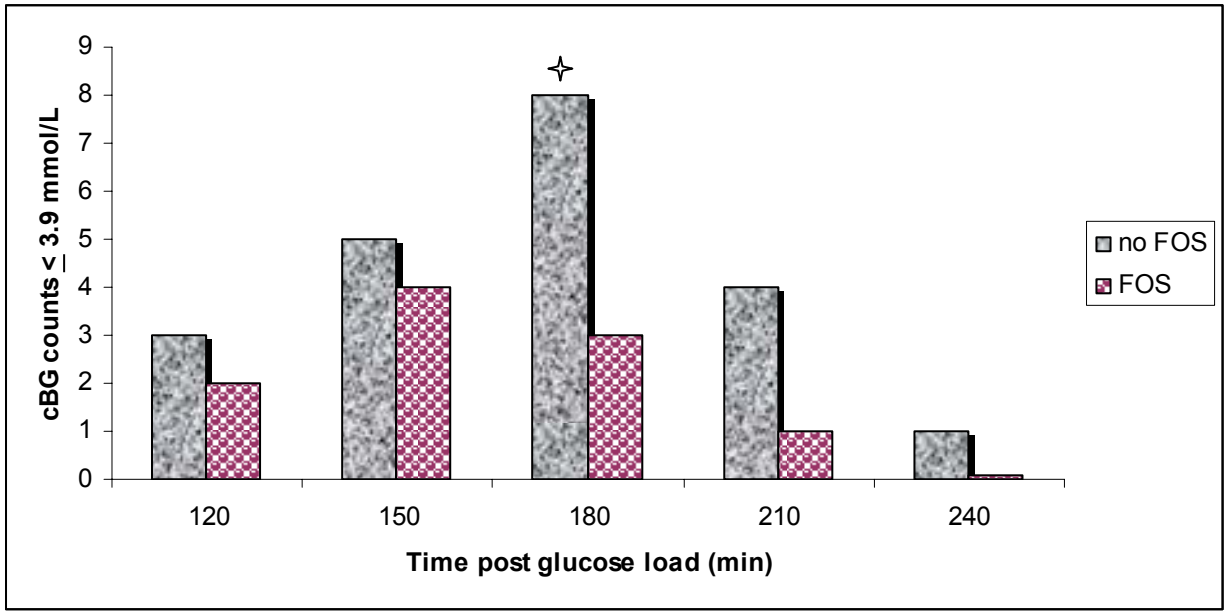


Figure 7. Proportions of subjects that during 120 - 240 minutes had cBG ≤ 3.9 mmol/L in the 4h OGTTs following each intervention sequence.



✧ : $p \leq 0.05$

Appendix A

Food plan app. 1800 kcal

Breakfast

1 fruit or 1dl orange juice

2 slices whole kernel bread or 4dl oatmeal porridge with water or 1dl müesli

1 teaspoon (ts) soft margarine or 2ts diet margarine or 10 pieces unsalted nuts

2 slices diet cheese

1 glass of skimmed milk

Vegetables as much as you like

Coffee/tea without sugar

Lunch

2 slices whole kernel bread

1ts soft margarine or 2ts diet margarine

App. 50g fish or meat low in fat

Vegetables as much as you like/salad

1 glass of skimmed milk or 1 portion of yoghurt (Yoplait 0.1%)

1 fruit

Coffee/tea without sugar

Snack

1 bagel or 2 crispbread

1ts soft margarine or 2ts diet margarine

2 slices diet cheese

Coffee/tea without sugar

Dinner

App. 120g low fat meat or any kind of fish or poultry without skin

3 boiled potatoes or 2dl boiled rice/pasta/beans

3/4dl dressing

1 tablespoon (TS) olive/raps oil

1 portion boiled vegetables

1 portion salad

1 TS dressing or vinaigrette

Water/diet soda

Dessert: 1-2dl fresh/frozen berries or 1 fruit

Supper

1 slice whole kernel bread or 2 crispbread

1ts soft margarine or 2ts diet margarine

1 slice diet cheese or diet melted cheese

Vegetables as much as you like

Tea/water/diet soda

Appendix B

Food plan 2100-2200 kcal

Breakfast

1 fruit

1.5dl müesli with fruits, nuts and 2dl skimmed milk

or

2 slices whole kernel bread

Soft margarine, low fat meat, raw vegetables

1 glass of skimmed milk

Coffee/tea without sugar

Lunch

2 slices whole kernel bread

2ts soft margarine

Cold cuts of fish or meat low in fat

Vegetables as much as you like

1 glass of skimmed milk

1 fruit

Coffee/tea without sugar

Snack

1 fruit

0.5dl unsalted nuts

Dinner

App. 150g low fat meat or any kind of fish or poultry without skin

3 boiled potatoes or 2dl boiled rice/pasta/beans

1dl low fat dressing

1TS olive/raps oil

1 portion boiled vegetables

1 portion salad

1TS vinaigrette

Water/diet soda

Dessert: 1-2dl fresh/frozen berries

Supper

2 slices whole kernel bread

1ts soft margarine

2 slices diet cheese

Vegetables as much as you like

Tea/water/diet soda

Appendix C

S P Ø R R E S K J E M A

Dato:

Dine initialer:

1) Har du diabetes type 1 eller type 2 i nær familie (mor, far, søsken, barn)?

NEI: ___

Hvis JA, spesifiser relasjon og type 1 eller type 2:

_____

_____

2) Har du vært innlagt på sykehus etter 01.05.2008?

(Svar Ja/Nei i grå  *boks)*

Hvis JA, for hva:

_____

_____

3) Hvor ofte opplever du symptomer på lavt blodsukker?

a) Aldri ***(→ gå til spm. 5)***	
b) 3 eller færre ganger pr måned	
c) Ukentlig	
d) 3 eller færre ganger pr uke	
e) Daglig	
f) Flere ganger daglig	

Vennligst spesifiser hvilke symptomer du har: *(Sett kryss for å bekrefte, flere kryss mulig)*

a) Svimmelhet	
b) Skjelving	
c) Hodepine	
d) Svette/kaldsvette	
e) Irritabilitet	
f) Sult	
g) Søvnig på dagtid	
h) Blekhet	
i) Hjertebank	
j) Konsentrasjonsvansker	
k) Annet:	

4) Har du noen gang tatt kontakt med lege i forbindelse med symptomer på lavt _____ **blodsukker?** *(Ja/Nei)*

5) Har du i løpet av den siste måneden hatt følgende plager?

	Mye plaget	**Litt plaget**	**Nei**
a) Luft i magen			
b) Rumling i magen			
c) Forstoppelse			
d) Diaré			
e) Svimmelhet			
f) Hodepine			
g) Aggressivitet			
h) Skjelvinger			
i) Sult mellom måltider			
j) Smerter generelt			

6) Hvor mange hovedmåltider spiser du hver dag? *(Sett strek <u>under</u> riktig svaralternativ)*

1 2 3 4 5 6 7

7) Hvor mange delmåltider/snacks spiser du hver dag? *(Sett strek <u>under</u> riktig svaralternativ)*

1 2 3 4 5 6 7

8) Røyker du? *(Ja/Nei)* _____

Hvis JA, hvor mange år har du røkt?_____
Hvor mange sigaretter har du røkt daglig i gjennomsnitt?

Hvis NEI, har du tidligere røkt daglig? *(Ja/Nei)* _____

Hvor mange år er det siden du sluttet: _____

Hvor mange år til sammen røykte du daglig: _____

Hvor mange sigaretter røykte du daglig: _____

9) Drikker du alkohol? *(Ja/Nei)*

Hvis JA, hvor mange glass drikker du vanligvis i løpet av 2 uker:

ØL: ___ VIN: ___ BRENNEVIN: ___

10) Arbeidsforhold (kryss av for nåværende situasjon):

I full jobb: ___

Deltidsjobb (angi %): ___

Uføretrygdet (angi %): ___

Pensjonist: ___

Arbeidsledig: ___

Hjemmeværende: ___

Student: ___

11) Familieforhold (kryss av for nåværende situasjon):

Gift/samboer: ___

Skilt: ___

Enke/enkemann: ___

Enslig: ___

12) Hva heter din fastlege? _____

13) Har du noen form for matvareallergi? ☐ *(Ja/Nei)*

Hvis JA; vennligst spesifiser: _____

_____

14) Vektlegger du et sunt kosthold? *(Sett strek under riktig svaralternativ)*

Svært mye mye middels lite svært lite

15) Hvor mye veide du for 1 år siden? *(Angi antall kg)*:_____

16) Hvor mange kopper kaffe (ca 2 dl) drikker du hver dag? *(Angi antall):*_____

17) Hvor mange kopper te (ca 2 dl) drikker du hver dag? *(Angi antall):*_____

18) Hvor ofte spiser du følgende matvarer?

	Daglig	*Ukentlig*	*Månedlig*	*Sjelden/ aldri*
a) Linser/Bønner				
b) Fullkornsbrød/knekkebrød				
c) Porsjon av 400 g grønnsaker				
d) Frukt				
e) Frokostblanding/havregryn				
f) Nøtter				

19) Hvordan vurderer du din helse? *(Sett strek under riktig svaralternativ)*

Meget god God Verken/eller Dårlig Svært dårlig

20) Medisiner; vennligst fyll ut navnet på, styrken på, og hvor ofte du tar medisiner nedenfor.

1. _____

2. _____

3. _____

4. _____

5. _____

6. _____

7. _____

8. _____

9. _____

10. _____

21) Kosttilskudd; (f.eks. omega-3, multivitamin). Vennligst fyll ut navnet på, og antall tabletter nedenfor.

1._____

2. _____

3. _____

4. _____

5. _____

6. _____

7. _____

22) Hvor mange timer sover du pr natt på hverdager i gjennomsnitt? *(Angi*

*antall):*_____

23) Hvor mange timer sover du pr natt i helgen gjennomsnitt? *(Angi*

*antall):*_____

24) Har du drevet noen former for mosjonsrelaterte aktiviteter <u>de siste syv dager</u>? ☐ *(Ja/Nei)*

25) Hvis ja, hva gjorde du, hvor mange ganger og hvor lenge drev du med denne (disse) aktivitetene?

			Intensitet		
	Antall ganger (siste 7 dager)	**Minutter totalt**	**Lett**	**Moderat**	**Tungt**
a) Spasertur (rolig gange)					
b) Turgåing (rask gange)					
c) Bowling					
d) Sykling					

e) Gymnastikk/trim					
f) Svømming					
g) Dans					
h) Styrketrening					
i) Anstrengende husarbeid					
j) Annet:_____					

26) Gjør du disse aktivitetene regelmessig? *(Ja/Nei)*

Hvis JA, hvor mange ganger i uken driver du en eller flere av disse aktivitetene?

Aktivitet:	**< 1 gang**	**1 gang**	**2 ganger**	**3-4 ganger**	**> 4 ganger**

27) Bruker du trapper fremfor heis/rulletrapp?

Ja ☐

Nei ☐

Av og til ☐

28) Dersom du er i arbeid, har du en stillesittende jobb? *(Ja/Nei)*

Hvis NEI, hvor mange timer beveger du deg hver dag på jobb?

(Angi antall):_____

29) Hvor mye tid bruker du gjennomsnittlig pr dag på disse aktivitetene i fritiden?

	Minutter Man - Fre	**Minutter helg/ fridager**
TV		
Lese		