Postprandial blood glucose, hormones and food intake

-A clinical trial

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Abbreviations and definitions

AUC= Area Under the Curve

BMI= Body Mass Index

CVD= Cardio Vascular Diseases

High (low) glycemic food= a food giving a high (low) postprandial increase in the blood glucose concentration

IAUC= Incremental Area Under the Curve

IQR= Inter Quartile Range

GHSR= Growth hormone secretagogue receptor

GI= Glycemic Index

GL= Glycemic Load

REE= Resting Energy Expenditure

SD= Standard Deviation

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The most exciting phrase to hear in science, the one that heralds new discoveries, is not 'Eureka!' (I found it!) but 'That's funny ...' Isaac Asimov

Abstract

Background: Several aspects of the postprandial effects of meals need further investigation. In particular, we were interested in focusing on whether the glycemic effect of meals is related to the serum concentration of hormones known to be involved in appetite regulation, and to hunger and food intake.

Objective/research questions: Will the intake of two lunch meals differing in the carbohydrate source, have different effects on a) the postprandial blood glucose concentration and b) serum levels of hormones related to appetite: insulin, ghrelin, leptin and growth hormone? Will possible differences in these variables be reflected in a) hunger during the next five hours and b) food intake at the next meal?

Methods: Eleven overweight male adults were evaluated on two separate occasions in a cross over fashion. The subjects consumed at noon either a meal with an anticipated low or high glycemic effect (meal L and H respectively). The meals were similar in energy and fat content, taste and energy density, but had major differences in carbohydrate sources (lentils or potato as main sources of carbohydrate, respectively). Meal H and L differed also in protein, carbohydrate and fibre content. During five hours after the lunch meal, hunger, plasma blood glucose and serum hormone levels were measured. Five hours after lunch, the ad libitum food intake was determined at a single meal.

Results: Glucose levels were remarkably stable after meal L and did not increase by more than 13 % to peak, whereas glucose levels after meal H increased by 52 % to peak and reached a nadir that was 8% lower than baseline values. There were significant differences after the two test meals in plasma ghrelin (H>L), growth hormone (H>L) and insulin concentration (H>L), but no differences in hunger or food intake were observed.

Conclusion: Lunch meals with appreciably differing postprandial glycemic effects do not affect hunger or food intake in the next meal in overweight adults in this

particular setting, in spite of differences in the serum level of appetite regulating hormones.

1. General background

The prevalence of obesity (BMI $\geq$ 30 kg/m^2) has risen greatly world wide during the last 25 years. The WHO characterizes the increase in obesity as an escalating global epidemic, affecting both affluent and non-affluent countries. In the U.S., which is one of the worst affected countries in the world, a staggering 60 %[1] of the adult population is overweight (BMI $\geq$ 25 kg/m^2), with obesity rates approaching 20% and 15% for adults[2] and children[3] respectively. Even more alarming is the rapidity of the increases in childhood obesity with prevalence having increased in a range from 2 to more than 4 fold in the worst affected countries over the last 25 years[3]. In Norway the problem is not as alarming. Yet, during approximately the last 30 years, there has been an increase in body weight of 10 kg for 40-42 year old men and 4 kg for 40-42 year old women, a 3 fold increase in obesity rates for men in the age of 50-54 years[4] and a height adjusted increase of 3 kg in body weight in 9-year-olds (L.K.Heggebø, personal communication, October 2003). Thus, there is a need for the problem to be taken seriously also in Norway.

Overweight is associated with increased mortality and is an independent risk factor for diabetes and cardiovascular disease. For instance, a man with a BMI of 32 has an 11 fold increased risk of diabetes compared with a man of normal weight, and a man with a BMI above 35 has a more than 40 fold risk[5]. Diabetes in turn increases the risk for cardiovascular diseases (CVD) and other comorbidities such as nephropathy, retinopathy and neuropathy. Additionally, overweight increases the risk for certain types of cancer, sleep apnea and osteoarthritis[4].

Traditionally, the most common way of dealing with obesity in health care has been to encourage the obese patient to do, in mechanistic terms, the opposite of what is assumed to cause excess weight, i.e.: to consume less food and spend more energy. With regard to diet the most common approach has been prescription of diets that provide an energy intake below that of energy expenditure, usually in the range of

3500-6500 MJ/d. Usually this is achieved using diet plans with fixed energy content, or by limiting the use of energy dense foods. Evaluation of the outcome of energy restriction interventions is difficult because few randomized trials have been done and various adjunctive interventions confound interpretation. However, although the effect of the prescription of energy restriction diets per se is difficult to evaluate, this evaluation might not be relevant, as no intervention study in the literature, whatever the method, seems to have been able to induce lasting weight loss[6] [1]. Furthermore, evidence for energy intake being a predictor of subsequent weight gain has not been found by studying the literature.

Thus, at present the evidence for the continued use of energy restricted diets is sparse. Despite this, the belief that energy restriction can induce sustained weight loss, or should be part of a weight loss strategy still seems to influence research[7] and clinical practice [8]. The continued prescription of energy restricted diets for weight control, despite lack of evidence for their effect, may partly be due to the self observed effects energy restriction or energy over-consumption have on body weight in the short term, and the belief that the increase or decrease in weight thus observed is relevant for the long term outcome. For the layman, but also for many clinicians, it may seem so logical that the obese are obese because they have overeaten, that evidence for this is not even sought. Yet, stating that overeating is a cause of obesity is a circular argument because only when an individual is fat can one say that an individual has overeaten; that lies in the very definition of overeating[9]. Notwithstanding, there is of course no doubt that when energy intake exceeds energy expenditure, an increase in body weight occurs. This is just a trivial observation however, and tells little about why the obese choose to eat more than they expend. An increase in body weight of a few kilos by eating more than one usually does, is not particularly relevant in evaluating what causes obesity; rather this may just be looked upon as a confirmation

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[1]As there are no apparent advantages associated with weight cycling, weight loss in this paper will only refer to lasting weight loss if other not specified. "Lasting" is defined as clinically relevant weight loss beyond two years since the start of the intervention.

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of the fact that it is possible to change the body weight to a certain extent by intentionally changing the energy intake. Concerning more long term effects, and changes by more than a few kilos, it is paramount to remember that body weight is tightly regulated. For instance, the imbalance between energy expenditure and energy intake in lean and obese individuals during a decade is typically less than 1 % [10]. Additionally, when deviating from the body weight an individual maintains without consciously restricting calories, body weight appears to be controlled by the same mechanisms, and to the same extent, in obese and normal weight individuals[11]. Under controlled conditions there are indications that the resistance towards body weight change increases proportionally the further one deviates from the baseline weight[11]. The resistance mechanisms operate in both directions: When body weight is increased by overfeeding, hunger is decreased and energy expenditure is increased. When body weight is decreased by underfeeding, hunger increases, and resting energy expenditure decreases. Unlike many other regulated biologic variables, such as blood pressure and electrolyte concentration in blood, body weight regulation is directly subject to voluntary control, i.e. one can use willpower to withstand hunger and thus loose weight. There are however no known reasons to us why the fact that a homeostasis mechanism, such as hunger, should be looked upon as a variable that should be rendered to the individual's willpower to control. Continued hunger in spite of energy surplus is a symptom of a malfunctioning body, and the body should be treated as such. Thus, if body weight deviates from its desired value, one should try to find the cause of this derangement, -not impede the body's attempts at reaching what it perceives as being the proper body weight.

The vacancy of evidence for a successful dietary weight loss regime has prompted the view that weight is controlled by genetics and that attempts to lose weight will engage a person in a battle with his body that he at the end will loose[12]. This seems too pessimistic given the large increase in obesity over the last few decades and the relative stability of the human gene pool: there has to be some factors in the

environment having caused this, and it is likely that modification of these factors will induce lasting weight loss in the obese.

With this at hand, it is evident that changes in the lifestyle and diet during the last decades can provide clues to the causes of obesity. It is widely believed that diet and physical activity are the two single most important factors to evaluate in this respect. While it is well documented that physical activity generally has a weight reducing effect[4,13], it is highly uncertain to what extent a reduction in physical activity level over the last few decades can explain the increase in obesity. First of all good figures for the secular changes in physical activity are lacking, and secondly, to our knowledge, no long term intervention studies evaluating the outcome of modest increases in physical activity have been conducted. The evaluation of modest increases seems to be of most relevance as large increases may not be possible to achieve on a population level, and in spite of the lack of good figures, physical activity levels do not appear to have declined dramatically during the last decades[14]. Interestingly, a recent prospective study[10] does not support the contention that a low level of physical activity may lead to obesity development.

With regard to diet, large changes appear to have occurred in the developed countries not only during the last century, but also during the last 2-3 decades. First, during the last 2-3 decades, there has been a transition to production of foods which can meet the needs of a more hectic lifestyle. There has been an increase in the production of processed foods for fast preparation and consumption at home, but also the availability and consumption of fast foods and snacks outside the home, seem to have increased. Secondly, the diet appears to yield higher levels of postprandial glycemia[15]. Thirdly, with the focus on fat being important for the prevention of CVD and obesity, there has been a large increase in the number of low fat products. Concordantly the intake of fat has decreased [16,17].

In line with these changes in diet and the concomitant increase in obesity, a diet that gives high postprandial blood glucose values has been proposed as a cause of

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obesity[15]. Conversely, a diet that gives relatively low postprandial blood glucose values has been proposed as a treatment for obesity. This paper has this line of thought as a background hypothesis, and the present study aimed at elucidating a specific mechanism related to the hypothesis.

1.1 Investigating the causes of obesity

Trying to pinpoint the exact mechanisms behind the development of obesity is a difficult task as body weight is a sliding scale with obesity at one end, and under weight at the other. Thus defining obesity or overweight using cut-off points such as a BMI-value of 25 kg/m^2 or 30 kg/m^2 has of course no practical importance with regard to finding the mechanisms behind obesity; no clear cut changes occur as the BMI exceeds the partially arbitrary 25 kg/m^2 - or 30 kg/m^2 -mark, which serve as cut off points for overweight and obesity respectively. Therefore, the investigation of long term body weight regulation is all about finding out why the factors that promote weight gain outweigh the factors that prevent it. For instance, short-term studies that show that certain factors are conducive to higher energy intake in a meal or during a day may say very little about the effect of those factors on long term body weight regulation, as the body may fully compensate for the increased intake in the long term. The key issue is whether or not such a factor gives any input to the overall sensors of energy status in the body. Even though all such factors were to be identified it would still not suffice to say what the sum of these factors would mean for an individual's body weight. Only intervention studies can reveal what will actually happen. Exploring mechanisms is important however, as they may guide the way to identifying those factors that are conducive to weight gain, although their relative importance is hard to quantify. If for instance a hormone can induce hunger by intravenous administration and a certain type of meal increases the level of this hormone relatively more than another type of meal, then one has a starting point for further investigation. If then, long term studies show that lower levels of this hormone

persist on a certain diet and weight loss also ensues, it would seem that one has a factor which could play a part in the regulation of body weight.

1.2 The brain and adiposity signals[2]

Due to the important role the brain plays in body weight regulation[18], it seems appropriate that a discussion of the causes of obesity includes how the brain integrates signals of energy sufficiency or insufficiency, and how this causes decreased or increased energy intake and/or energy sparing (see Figure 2). The major integration centre in the brain for the regulation of eating and body weight is the hypothalamus. Vagal afferents and various hormones act upon the arcuate nucleus of the hypothalamus, thus informing the brain of the energy status. Insulin, leptin, and ghrelin have receptors in the arcuate nucleus and all of these hormones affect adipose tissue mass[18,19]. (Other substances that act upon the hypothalamus are not commented in the present work, as only these three hormones seem to be long term regulators of adipose tissue mass, as will be discussed in later chapters.) Within the arcuate nucleus insulin and leptin both seem to exert their actions primarily through the melanocortin system, while ghrelin appears to exert its actions primarily by increasing the expression of neuropeptide Y and Agouti related protein[20]. The integrated perception of adiposity status by the arcuate nucleus is passed on to the paraventricular nucleus, which in turn processes this information into autonomic effects and behavioural responses related to energy conservation/expenditure and increased/reduced energy intake. Insulin and leptin generally reduces[21,22], while ghrelin increases[23] energy intake when administered intracerebroventricularly in

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[2] The brain and its relation to body weight regulation is only briefly discussed. The intricate mechanisms operating in the brain with regard to body weight regulation is not intended to be a central theme of the paper, but a basic overview of the brain's role in body weight regulation will aid the understanding of the central hypotheses in this paper.
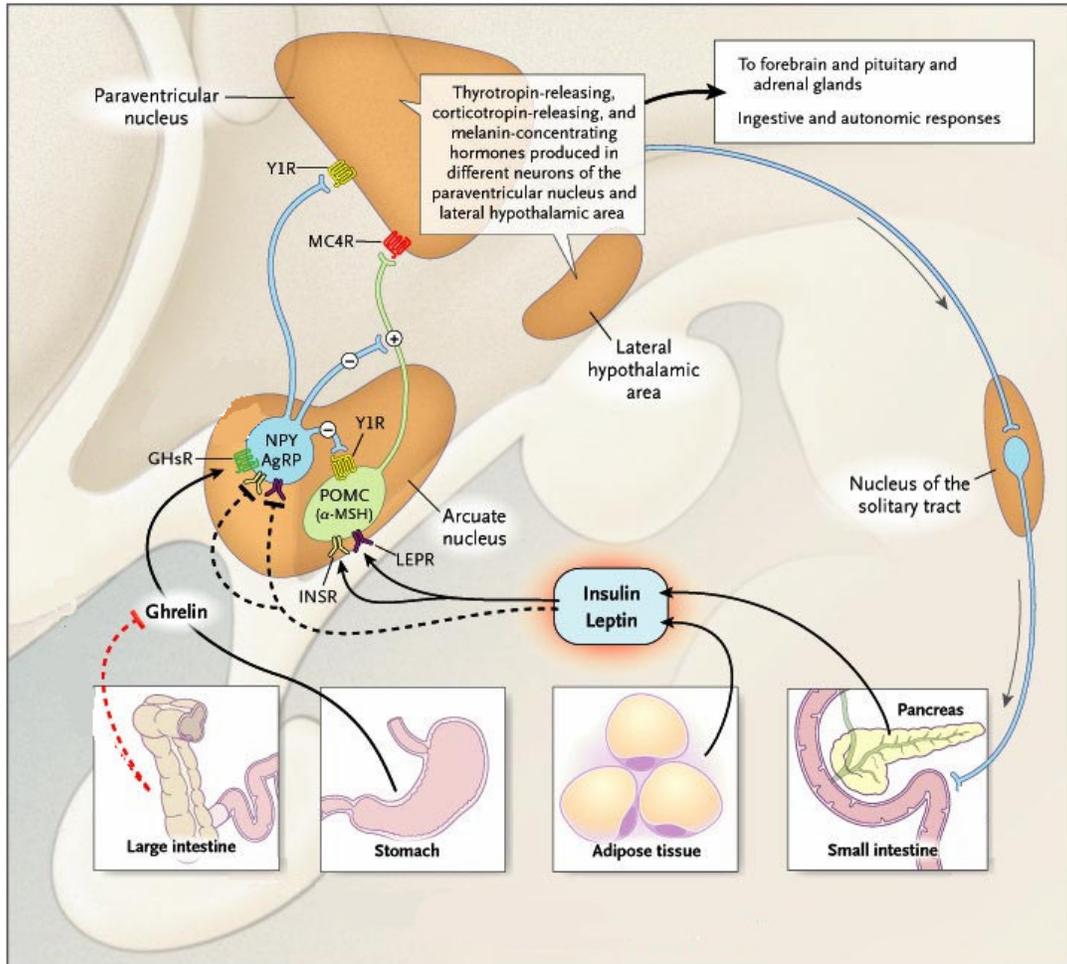
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rodents.

Figure 1. *Interactions between hormonal fat mass signals and neural pathways that regulate food intake and energy expenditure, as outlined by Korner et al[20]. Dashed lines indicate inhibitory effects, and the solid lines stimulatory effects. Y1R denote the neuropeptide Y (NPY) receptor, MC4R melanocortin 4 receptor, GHsR growth hormone secretagogue receptor, AgRP agouti-related protein, POMC proopiomelanocortin, α-MSH α-melanocyte–stimulating protein, LEPR leptin receptor, and INSR insulin receptor (Slightly modified from Korner et al[20]).*

1.3 Adiposity signals and their relation to diet

According to Schwartz et al[18], an adiposity mediator, i.e. a substance that informs the brain about fat mass status, is a substance that fulfils the following criteria: It

should circulate in direct or inverse proportion to the amount of adipose tissue mass and it should cross the blood brain barrier and interact with receptors and signal transduction systems in neurons in the brain known to regulate energy homeostasis. Exogenous administration of the compound should affect food intake and/or metabolic rate, and repeated infusions should alter body-fat mass if continued for some time. Blockade of the signal should exert the opposite effects. To this date there are only three known compounds that fulfil these criteria: insulin, leptin and ghrelin[19].

INSULIN

Insulin is the prime energy storing hormone in the body, and together with glucagon it plays a key role in the integration of the metabolism between adipose tissue, skeletal muscle and the liver. Without insulin blood sugar levels increase dramatically, lipolysis is increased and protein uptake by the cells is decreased.

Increments in the blood glucose level or amino acid level in the blood after a meal are the two single most important triggers of insulin secretion. With regard to carbohydrate type, high glycemic meals stimulate more insulin secretion than low glycemic meals because of relative postprandial hyperglycemia. This larger insulin secretion may in turn cause insulin resistance, as demonstrated by decreased whole-body glucose disposal after insulin infusion under euglycemic conditions in humans[24]. Interestingly, primary hyperinsulinemia produced by insulin treatment of normal rats lowered insulin sensitivity of muscle but not of fat[25], as measured by increased insulin-stimulated glucose utilization index, increased de novo lipogenesis and glycogen synthesis. This would promote redistribution of energy substrates to adipose tissue, and if other effects of insulin are upheld, lead to the same adiposity signalling by insulin to the brain, although qualitative changes have occurred with regard to its energy storing effects. Additionally, Rodin et al[26] showed that hyperinsulinemia stimulates appetite, irrespective of blood sugar level, and

Velasquez-Mieyer et al[27] showed that reduction of hyperinsulinemia reduces the preference for high-carbohydrate foods. Thus, the consumption of high carbohydrate foods may lead to a self-perpetuating cycle of increasing hyperinsulinemia and increased preference for foods that are strong insulin stimulators. Based on findings from a recent study on severely obese adults, there are indications that these effects of insulin may bear relevance for long term effects of hyperinsulinemia on body weight. In that study, suppression of insulin secretion for 24 weeks significantly reduced body weight[27] (122±4.1 vs. 119.2±3.9 kg, P< 0.01). In prospective, observational studies however, it is not clear whether high insulin secretion can predict subsequent weight gain. Whereas in four studies hyperinsulinemia actually predicted a decrease in weight gain[28-31], two other studies came to the opposite conclusion[32,33]. Because of the observational nature of these studies, and the fact that insulin was measured at baseline only, no certain inferences on cause and effect can be drawn from these studies however. Individual increases or decreases in insulinemia from baseline over a period of time and their relation to weight change would say more about the causal role of hyperinsulinemia in obesity, but such measurements have to our knowledge not been carried out.

LEPTIN

Leptin is the 167-amino acid product of the ob-gene and is a hormone secreted primarily by white adipose tissue. The ob-gene was identified and sequenced by Zhang et al by positional cloning in 1994[34]. Lack of leptin production causes severe obesity in mice[34] and humans[35], and the correlation between percentage body fat and serum leptin concentrations is strong both in obese and normal-weight subjects[36]. Short term fasting however decreases leptin levels more than what would be expected from reduction in fat mass alone, implying that leptin is affected by factors not related to adipocyte size and content as well. Leptin's 24 hour pattern shows a nadir after noon and a peak after midnight during normal sleep/wake and feeding cycles[37]. When controlled for the sleep/wake and feeding cycle however, leptin appears to be less affected by circadian rhythm than by food intake[38]. Thus the

observed increases in leptin during night time could be the result of the cumulative effect of meals during day time.

Leptin does not seem to affect hunger acutely[39]. Chronic infusion of leptin has produced weight loss in diet induced obese[40] mice and ob/ob mice[41]. The first intervention study in humans using recombinant leptin induced weight loss in obese and lean adults[42]. Later studies have been disappointing however[43,44] and leptin in its current form is now abandoned as an obesity treatment (C. Hukshorn, personal communication, September 2003).

A possible explanation for the disappointing results is that leptin may primarily be an anti-undernutrition substance rather than an anti-obesity substance. Thus, as long as undernutrition is prevented leptin may not have further major influences on the amount of energy stored in the adipose tissue, because on leptins behalf "its job is done" as long as energy stores are maintained at a level deemed sufficient for the handling of possible subsequent energy deficits in the diet[45].

Differences in diet composition affect leptin levels. High fat diets and low glycemic diets stimulate less leptin during 24 hrs. relative to low fat, diets that have a higher glycemic effect [46,47].

After acute feeding a change in leptin usually takes more than 4 hrs to reach statistical significance [38]. Although leptin levels are relatively slow to change after short term influences such as single meals, different leptin responses have been observed between meals differing in macronutrient ratio. Frayn et al[48] showed that a carbohydrate rich meal increases leptin levels postprandially, while after a fat rich meal, plasma leptin decreases. To our knowledge the effects of meals differing in glycemic effect have not been evaluated.

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GHRELIN

Ghrelin, a 28-amino acid peptide discovered in 1999[49], stimulates appetite more than any other known agent produced or administered peripherally[50]. It was discovered during the search for a ligand for the growth hormone secretagogue receptor (GHSR). Later it has been shown that ghrelin has numerous other effects, most of which act to promote weight gain: it can increase food intake[50], and it can decrease metabolic rate[51], sympathetic nervous system activity[52] and fat catabolism[52]. Ghrelin is synthesized primarily in the stomach and the small intestine[53] and it seems to exert most of its effects by acting as a link between the gastrointestinal tract, the hypothalamus, and the pituitary.

Its levels are negatively correlated with percentage body fat[54] and are increased upon energy restriction[55]. Its levels are decreased by glucose intake[55], hyperglycemia[56], somatostatin[57], oxyntomodulin[58] and PYY[59]. Ghrelin in turn blunts arginin-induced insulin increases[60] and reduces insulin levels transiently[60]. Chronic infusion of ghrelin in rats induces severe obesity[61], and conversely, blockade of ghrelin signalling in the brain can cause weight loss[62]. In addition, ghrelin seems to signal meal initiation, based on the finding that there is an increase in ghrelin levels shortly before meal onset, followed by a decline within an hour after the meal [63]. Interestingly, ghrelin does not only seem to affect food intake in a transient manner. After intracerebroventricular injection of ghrelin in rats, food intake is increased in the following hour but this is not compensated for during the following 23 hours, with cumulative food intake during 24 hours being larger after ghrelin injection than after saline[23]. In a recent study[64] however, deletion of the ghrelin gene did not affect body weight in mice, indicating that ghrelin may not be a critical factor in long term body weight regulation.

In humans ghrelin is suppressed by meals in lean but not obese subjects[65], indicating that when ghrelin levels already are relatively low, a further decrease is inhibited.

Unfortunately, when the relation between consumption of meals and levels of ghrelin has been investigated, test meals have often not been described in detail, implying that effects observed may have been different with different characteristics of the meals. Of relevance to the present paper, studies that have examined the effects of meals differing in glycemic effect on ghrelin levels have not been found in the literature. The fact that on a high fat diet ghrelin levels are lower relative to a high carbohydrate, low protein diet[66], may indicate that low glycemic meals may not exert a strong suppression on ghrelin levels.

1.4 Postprandial blood glucose: regulation and physiological significance

Glucose is, in addition to fat, the most important fuel for the human body. The brain, retina, the erythrocytes and parts of the kidney and gonads are obligate users of glucose as fuel, and without glucose there is a rapid decline in the function of these tissues. Understandably, blood glucose is a tightly controlled variable. Its regulation involves the central nervous system, endocrine signals acting on pancreatic cells, and glucose utilization by different tissues. When fasting, and after the postprandial phase blood glucose oscillates within a level of about 4 to 6 mmol/l. In daily life, several factors influence this homeostatic system, resulting in oscillations both towards lower and higher blood glucose levels. Hypoglycaemia, when severe enough, results in death in a short time, whereas fluctuations of similar magnitude in the other direction, as measured in mmol/l glucose, do not give any appreciable negative acute effects. Conceivably, there are many blood glucose raising hormones, but only one blood glucose lowering one. Among hormones increasing blood glucose levels are epinephrine, glucagon, growth hormone and cortisol, and the sole hormone that lower it is insulin. Whereas for instance physical activity and stress influence blood glucose levels, in healthy humans the largest fluctuations are most often seen postprandially,

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caused by the consumption of meals containing carbohydrate. A major determinant of postprandial blood glucose levels is the rate of digestion and absorption of carbohydrate consumed in a meal, with postprandial glucose levels increasing with increasing digestion and absorption rates.

1.4.1 Digestion and absorption of carbohydrate

Carbohydrate is the only nutrient that elevates blood glucose directly, and therefore type and amount of carbohydrate are two major factors that determine postprandial blood glucose increments. The physiological response to meals, and thus to carbohydrate, starts before food is ingested, due to olfactory, visual or cognitive factors. This response is reflected in increasing levels of insulin, and increased secretion of saliva and gastric juice, to mention a few changes. On entrance in the mouth the enzymatic and mechanical digestion of complex carbohydrates and disaccharides starts. Single sugars are not enzymatically digested. Amylase from the salivary gland starts the breaking of the bonds between single sugar molecules in starch, but the enzymatic digestion is halted upon entrance in the stomach, due to the acid milieu encountered there. In the small intestine pancreatic amylase and brush border enzymes break most of the complex carbohydrates into smaller molecules; mainly glucose, galactose and fructose. These molecules are transported into the enterocytes. Thereafter the sugar molecules are released into the portal vein, and some of the sugar is taken up by the liver before entrance into the systemic circulation. The glucose that escapes uptake by the liver is largely what causes the postprandial rise in blood glucose concentration which can be measured in blood samples from veins or finger capillaries. This glucose is subsequently extracted by different tissues.

Differences in the rate of digestion and absorption of dietary carbohydrate depend upon the structure of the carbohydrate, other macronutrients present in the same meal, pH of the meal and factors that limit the digestive enzymes' access to the glycosidic bonds between the individual sugar molecules, such as non-nutritive factors (including antinutrients), fibre, grain capsules, how tight the sugar molecules are

packed together, the degree of hydration, and, possibly, yet unidentified factors. When comparing different starchy foods the perhaps most important factor determining digestion rate is the starch structure. The higher the amylose to amylopectin ratio, the slower is the digestion rate [67]. A major reason for this is probably that amylose is less susceptible to enzymatic attack. The relatively lesser enzyme accessibility is believed to be due to the linear structure of amylose, which is associated with a higher degree of hydrogen bonding, and the increased number of starch-lipid complexes in amylose relative to amylopectin[67].
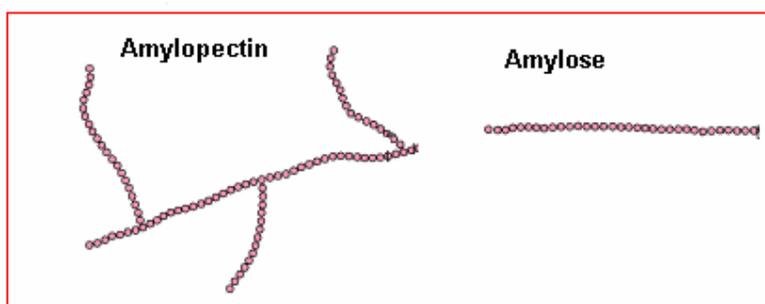

Figure 2. *Structure of the polysaccharides amylopectin and amylose ,which both consist entirely of glucose molecules. The glucose molecules in both polysaccharides are joined by α(1→4) bonds, but amylopectin also contains α(1→6) bonds at the branching points.*

Slower digestion of carbohydrates not only reduces postprandial glycemia, but may also have effects not related to the glycemia, but to the longer transit time of these foods through the gastrointestinal tract. When the intestines are in contact with food, the secretion of several enteric hormones is altered, some of which have effects related to meal termination, hunger and satiety. It is therefore possible that the longer the transit time, the stronger will the satiety signals be, and thus the time to the next meal may also be longer and/or the next meal will be smaller. However, little is known regarding the magnitude of the differences in levels of these hormones in response to carbohydrates with different transit times.

1.4.2 Adverse effects of hyperglycemia

Chronic hyperglycemia is strongly linked to microvascular complications of diabetes mellitus, including neuropathy, retinopathy, and nephropathy. Additionally, hyperglycemia has been linked to macrovascular disease[68]. Whereas evidence for adverse effects is less clear for *postprandial* elevations in blood sugar concentration, there is no established threshold for hyperglycemia under which adverse effects do not occur[69]. Indeed, high postprandial blood glucose levels have been linked to various diseases and derangements. In a European cohort study[70] the subjects in the highest quintile of blood glucose level 2 hours after a glucose tolerance test had an odds ratio of 1.6 for mortality, and a meta regression analysis of the relationship between postprandial hyperglycemia and incident cardiovascular events showed that postprandial hyperglycemia is a risk factor also in non-diabetic individuals[71]. These studies cannot confer evidence that elevated postprandial glucose levels are causally implicated in atherogenesis, in particular because a high 2 hour glucose value may first of all reflect a prediabetic state, which is associated with higher CVD-risk [72]. However, Temelkova-Kurktschiev et al[73] found that postprandial glycemic spikes were independently and positively correlated with intima-media thickness even when adjusted for 2 hr glucose values in healthy individuals. This makes a causal relationship between high postprandial blood glucose and CVD more likely.

The possible mechanisms for the adverse effects of hyperglycemia are discussed below. Primarily acute effects will be discussed here, but with occasional references to chronic effects where appropriate. Mechanisms of possible chronic effects on obesity development will be discussed in later chapters.

Mechanisms of direct effects

The mechanisms underlying the pathologic effects of hyperglycemia are related in part to *oxidative stress*, *structural changes such as glycosylation*, and *metabolic alterations*. Of special relevance to postprandial hyperglycemia, adverse effects on endothelial function and other CVD-related outcomes occur rapidly after meals that induce high postprandial blood glucose levels in healthy subjects[74] and in diabetics[75]. These effects can be prevented by the co-administration of antioxidants[74]. Eating antioxidant-poor meals that give high postprandial glycemia several times a day could thus chronically challenge the integrity of the endothelium, and possibly increase the risk for CVD.

Hyperglycemia has also been linked to protein glycosylation[76], basement membrane thickening[77], impaired cellular immunity[78], cell cycle abnormalities[79,80] and apoptosis in heart muscle[81]. These are factors which all may contribute to CVD-development.

The effects that hyperglycemia have on insulin secretion and insulin action has been termed glucose toxicity[82]. Much evidence indicates that these effects play important roles in the development of insulin resistance and progressive impairment in insulin secretion, and thus may be a causative factor in the development of diabetes. For instance, as little as 24 h of hyperglycemia (15.6 ± 0.3 mmol) induced a 20% decline in the rate of insulin mediated glucose disposal in well-controlled type I diabetics[83]. Much lower, and more physiological increments in blood glucose levels (+ 2 mmol/l for 3 days) induced similar impairment in insulin action in healthy young subjects[24]. Conversely, tight glycemic control, independent of how it is achieved, enhances insulin action and insulin secretion in diabetics, and may be a reason for the improvements in insulin production associated with the honeymoon period (the period

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where there is a transient decreased demand for exogenous insulin) in newly diagnosed type I diabetics[82].

Additionally, consumption of meals that give high postprandial glucose levels increases the demand for insulin. This may be important with regard to the development of insulin resistance as insulin infusion alone can cause insulin resistance [24,84,85].

Mechanisms of indirect effects

Meals that give different postprandial glucose levels may differ widely in their hormonal and metabolic effects. A meal of normal size that gives high initial blood glucose increments, may stimulate twice as much insulin as that of an isoenergetic meal that gives relatively low blood glucose values[86]. This surge of insulin directs the body into an energy storing mode; insulin inhibits lipolysis and hepatic glucose production, and enhances lipogenesis and glycogenesis. A rapidly absorbed carbohydrate rich meal is for the large part absorbed within 2-4 hours, and thereafter the body must draw from its own energy stores to ensure that blood glucose levels are kept sufficiently high, unless another meal is consumed. After a meal that gives a high postprandial glucose level, the transition from an energy storing mode to an energy using one may be metabolically challenging, as the effects of the high insulin to glucagon ratio may persist longer than the postprandial period itself, thus limiting the access to stored fuels. In a study by Ludwig et al this mechanism was the likely cause for the increased hunger and energy intake observed after a high relative to a low glycemic meal. In that study there was a rapid decline in blood glucose concentrations, below the fasting value, and relatively large increments in the diabetogenic hormones glucagon, epinephrine, and growth hormone, after consuming the high glycemic meal[86].

1.4.3 Measures of the glycemic effect of foods

The method which has been used the most to measure the glycemic effects of foods, is the glycemic index (GI) as it is defined by the WHO[87]. The GI was originally introduced by Jenkins et al in 1981[88] as an alternative method for the regulation of the intake of carbohydrate rich foods in the diabetics' diet. Traditionally carbohydrate exchange lists had been used, but Jenkins et al proposed that this method may not reflect the physiological effect of foods. To better estimate the effects carbohydrate containing foods have on postprandial glycemia, the glycemic index classification was developed. Glycemic index is defined as the 2 hour incremental area under the blood glucose response curve (IAUC) after the intake of 50 grams available carbohydrate from a test food relative to the IAUC after intake of 50 grams of a control food (either glucose or white bread) is consumed. The area below the fasting value is ignored (Figure 3).
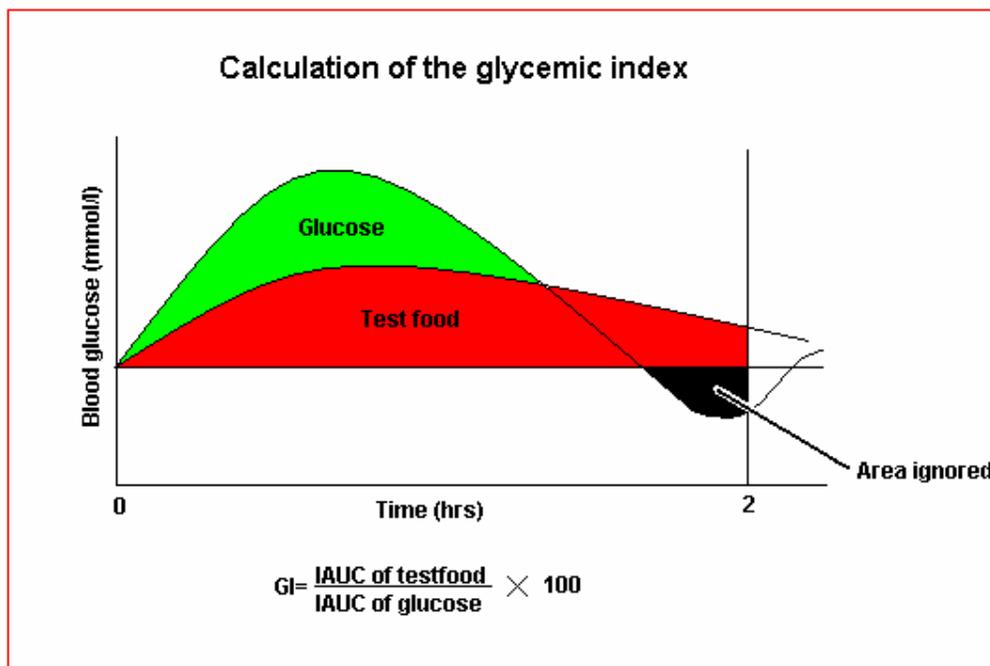

Figure 3. *Calculation of the glycemic index. IAUC=incremental area under the curve. Usually blood glucose levels are measured each 15 min during the first hour and each 30 in during the second hour, yielding a non-smooth line. Areas between each point of measurement are calculated using the trapezoidal rule.*

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To complement the GI-concept the Glycemic Load (GL)-concept was developed. GL is the product of the glycemic index (reflecting carbohydrate *quality*) and the *quantity* of carbohydrate ingested. This concept reflects the different impact of typical serving sizes of different foods on the blood glucose level. For instance: water melon has a high GI but a low GL, whereas ordinary rice has both a high GI and a high GL (Table 1):

Food	GI	GL	Carbohydrates per serving
Rice	70	35	50
Water melon	80	4	5

Table 1. Example of foods with different GI and GL values.

In Norway soft drinks, bread, potatoes, cakes, potato chips and rice are examples of high GI/GL foods regularly consumed by a large part of the population. Examples of different foods and their respective GI and GL are listed below (sorted by Glycemic Index) (Table 2).

Food	Glycemic index	Glycemic Load (100g)	Glycemic Load (per serving, grams per serving in brackets)
Rice, jasmine	109	31	46(150)
Potatoes, baked	85	17	26(150)
Water melon	72	4	4(120)
Corn flakes	58	70	21(30)
Whole meal rye bread	58	27	8(30)
Banana	52	10	12(120)
Apple	38	5	6(120)
Chick peas	28	6	8(150)
Lentils	26	3	5(150)
Cherries	22	2	3(120)

Table 2. *Various foods with their respective GI and GL values. GL values are based on typical serving sizes (in brackets) as defined by Foster-Powell[89], or per 100 grams of the food. As can be seen the rank of each food differs if based on GL based on 100 grams of edible portion, GL based on serving sizes, or if based on GI.*

The GI and GL values that can be obtained from tables of GI and GL for different foods primarily reflect the effect a specific food has on blood sugar under the specific conditions when doing tests for GI. As the GI is a relative measure, the GI is assumed to be the same also under other conditions as long as the reference food is also tested under the exact same conditions as the test food. However, the primary aim of focusing on a food's GI is to evaluate what effect that food has on the blood glucose, in absolute terms. When considering this, a range of factors may influence the impact different foods has on blood glucose level. These will be considered below.

Factors affecting postprandial glucose response

Nutrition status and diet

Fasting increases the blood glucose increments after the consumption of a meal containing carbohydrate, as compared to the well fed state. One study showed that after a prolonged fast glucose tolerance is greatly reduced as compared to an overnight fast[90]. Moreover, as compared to an overnight fast, glucose tolerance is improved if a meal containing carbohydrate has been consumed in the hours before a carbohydrate load. This is referred to as the Staub-Traugott effect[91,92] or the second meal effect[93]. Also, the quality of the first meal is a major determinant of second meal glucose response. For instance, when a low glycemic, high carbohydrate meal is consumed for hours before the second meal, glucose tolerance is improved relative to a high glycemic meal (with equal carbohydrate amount)[93]. The mechanism behind this effect appears to be linked both to the type and amount of carbohydrate, as indicated by the absence of any improved glucose tolerance after the consumption of a low glycemic, *low* carbohydrate meal compared to a, high glycemic, *high* carbohydrate one[94]. This suggests that the glucose tolerance in the hours after different meals is primarily affected by insulin/carbohydrate dynamics in the postprandial state, and not to overall energy status or other factors. In other words, four hours after a low glycemic, high carbohydrate meal the body is closer to being in

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an energy storing mode than after a high glycemic one, because after the high glycemic one, nutrient absorption is faster. Thus, the switch from utilizing nutrients from the intestine directly for energy production to drawing upon its own energy stores, comes earlier after a high glycemic meal. The consumption of a second meal four hours after a low glycemic one may thus be seen as a continuation of the first meal, whereas the consumption of a high glycemic meal as the first one, truly makes the next meal a separate event. While this first-meal-extension-effect may be part of the mechanism, there appears to be other factors which are involved as well, because glucose tolerance is improved even when a low glycemic meal is eaten as long a time as the evening before a standardized breakfast[95]. More studies are needed to clarify for how long the effects of a meal on subsequent glucose tolerance persist, and what factors in the meal that predict the subsequent glucose tolerance.

Considering more long term effects, after a period on a low carbohydrate diet, glucose tolerance may be reduced[96]. In other words, when the body is primed for the handling of glucose from the diet, be it due to inter-meal effects, or longer term adaptations, this appears to result in an improved glucose tolerance.

Exercise

Short bouts of physical exercise which do not lower glycogen, do not improve post exercise glucose tolerance acutely[97,98], although after a prolonged exercise bout, with a marked reduction in glycogen stores, the glucose tolerance is increased[99]. Exercise in the postprandial period however has a profound impact on the glucose response. Even light postprandial exercise can blunt glucose increments even after a high glycemic meal[100].

Age and gender

When adjusted for fat mass and lean body mass, age[101] does not appear to have a major effect on glucose tolerance. We have not been able to find literature which evaluates the impact of gender on glucose tolerance.

Time of day

Glucose tolerance appears to be reduced during the afternoon and evening[102] .

Medications

Various medications, such as corticosteroids and unselective β-blockers, can decrease glucose tolerance.

Accuracy of the glycemic index and the glycemic load, and practical application

Although the importance of avoiding high postprandial blood glucose levels is widely appreciated, the use of the glycemic index and glycemic load concept as a means of achieving this has been questioned. The critique has been centred on two main issues: the accuracy of the GI and GL values, and the practical application of the concepts. I will discuss these two issues further.

Accuracy of the glycemic index and the glycemic load

The concept of the GI is precisely defined[103]. The GI's for several seemingly similar foods can differ widely however. For instance, high amylose rice may have a GI as low as 37[67] and jasmine rice may have a value as high as 109[104]. Botanical variety does not by far explain the whole variability in the GI values however. In a recent interlaboratory study[105] the botanical variety issue was eliminated by testing the same foods in different laboratories. The mean GI values differed by up to 33.5 units for the

same food, a difference which must be considered to be rather large. The standard deviation for each food tested in the different laboratories was also large. Rice, with an average GI of 71, had a standard deviation which was in a range from 8.1 to 75.9 in the different laboratories respectively, implying that there is a need for better methods to reduce within-subject variation. A study that specifically evaluated the within-subject variation found that a total of four repeated tests were required to rank three different foods with GI's of 61, 79 and 100 correctly, in all of 12 subjects[106].

There is room for debate whether the glycemic index can be used to reflect the true effects of each food on glycosylation, insulin secretion, and other markers related to the glycemic effect of foods. While it is well documented that the GI to the very least provides a crude measure of glycemic effects of different foods, it says nothing directly about the *shape* of the blood glucose curve. For instance, it is not known whether a food which gives blood glucose values that reach higher peaks than other foods gives more adverse health effects than foods that yield a higher GI, but do not reach as high a peak, if such differences exist at all. Additionally, different diseases and conditions could differ with regard to whether the peak blood glucose or the GI is the prime indicator of adverse effects. This also complicates the use of the GL, as this concept tells even less about the shape of the curve. Ludwig[107] however, argues that GL's applicability is fairly good based on the following findings: (1)calculated GL can predict the glycemic response (i.e. 2 hr IAUC) to individual foods across a wide range of serving sizes and (2)in several epidemiological studies, GL is independently associated with important health outcomes. These findings do not assure however, that individuals choosing a low-GL diet consisting of a small amount of low-GI foods will have the same health outcomes as those choosing a low-GL diet consisting of a large amount of low-GI foods. For instance, a serving of two different foods with the same GL but different GI, gives the same IAUC, but other effects such as transit time through the gastrointestinal tract and the effects of continuous, long lasting absorption vs. rapid absorption of carbohydrate is not reflected by GL directly.

Foods are more often eaten in a mixed meal than on their own. Initially there were concerns that this would render the concept of the GI of limited utility in a normal diet[108,109]. Later studies have however shown that the glycemic response to mixed meals can be predicted with a rather good accuracy using standard methods[110,111]. This implies that other macronutrients do not affect the glycemic response appreciably in normal mixed meals.

The estimation of the GL of foods, based on the respective GI's, includes another factor which is subject to variation (the amount of carbohydrate in each food). Thus, the GL is a more inaccurate measure than the GI.

Practical application

The GI/GL is a tool which is developed to aid in food choice, and does not directly harbour information on any other aspects of the diet. Thus, the effects of the use of GI/GL are highly dependent on the way it is used. The skilled nutrition educator should be able to convert knowledge about the GI/GL into practical and feasible advice that will reduce a patient's glycemia without even mentioning the concept, while at the same time assuring that other aspects of the diet are not compromised. This can be done by focusing on which food types and what amounts of individual foods to be chosen, rather than focusing on each food's GL/GI, e.g. "eat more legumes and less white bread". As for the layman, a one-sided focus on the GI/GL's of foods may lead to unwanted changes in the diet, as with any other narrow approach, be it low-fat, high-fibre, or low calorie diets. This means that care should be taken that information on the GI/GL of a food comes hand in hand with a minimum of information on how to use it.

The fact that different botanical varieties of similar foods may have different GI-values is considered by some to be problematic[112]. An alternative view is that this

gives the consumer the possibility to choose better foods without making large changes in the diet.

Due to the uncertainties concerning the accuracy of the GI/GL, in the present work, the term glycemic effect or postprandial glycemic effect is used when relating to blood glucose levels after food intake.

1.4.4 High glycemic diet and obesity

The average glycemic effect in the diet appears to have risen in the US in recent years[113] and it is likely that this has happened in Norway as well, based on the fact that carbohydrate consumption has increased concomitantly with increases in consumption of sugar[16] and changes in food-processing technology. This raises the question whether the increase in the glycemic effect in the Norwegian population could be one of the factors that can explain the obesity epidemic. Several studies have addressed the issue, some of which will be reviewed here.

Short term studies in humans (single day studies)

Reviews that have evaluated the effects of low- vs. high glycemic meals in single day studies on satiety, hunger and food intake have come to different conclusions. A review by Raben concluded that there is no convincing evidence that low glycemic meals are beneficial in this respect[114], whereas other reviews are more positive[15,115]. Pawlak et al[116] criticized Raben's meta-analysis of short term studies on methodological issues and argued that several of the studies included in the analysis were either underpowered or irrelevant to the hypothesis under question. In particular, Pawlak et al noted that 19 of these studies did not demonstrate differences in glycemic responses, or energy content was not controlled. Therefore Pawlak et al argued that these studies should not have been included in the analysis. Based on these considerations Pawlak [116] et al re-evaluated Raben's meta-analysis and found that among 12 remaining studies, six reported a statistically significant result in favour of the low glycemic meal, 3 showed a trend in favour of the low glycemic meal, one reported no difference between meals, one reported a trend in favour of the high glycemic meal and none reported a significant result in favour of the high

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glycemic meal. Pawlak et al therefore concluded that meals with a lower impact on postprandial blood glucose levels may play a significant role in increasing satiety, reducing hunger or reducing food intake.

As illustrated by the different views as discussed above, the results from short term studies may not be clear cut, but it is evident that consumption of low glycemic foods relative to high glycemic foods has effects which to the very least are related to satiety and food intake under certain circumstances, and thus may play a role in long term body weight regulation. When evaluating the strength of the evidence from short term studies for effects of a low glycemic diet on body weight regulation, it is paramount to remember what a small surplus of energy intake which is needed at meals to gain several kilos of body weight over a longer period. Thus even half a bread slice with butter and spread (0,385 MJ) extra at a meal once a day for a year would amount to 3,8 kg extra body weight (under the hypothetical condition that all other factors are kept the same). Such small differences are not likely to be detected in single meal studies. All the more, this puts the study[86] that showed that the energy intake after a single high glycemic meal vs. a low glycemic meal was 2.6 MJ larger (or the equivalent of 3.5 bread slices with butter and spread), in a different light, and downplays the importance of studies which have not detected measurable differences. However, in most of the studies in this area the test meals have been given for breakfast. Little is known concerning the effects of a single meal eaten at lunch, on subsequent food intake. Usually lunch is eaten as the second meal of the day. This difference may influence subsequent food intake due to the second meal effect. Most likely this will lead to smaller differences in food intake, probably due to better regulation of blood glucose and, thus, better access to metabolic fuels, as outlined above.

Additionally, few of the studies have examined the effects of mixed, normal meals; the test foods have often been one separate food eaten alone, or they have not represented meals free living subjects are likely to choose.

Finally, few of the studies have included obese subjects. The inclusion of obese subjects is important because the obese might have responses to high glycemic meals which are different from the lean subjects' responses. Different responses to foods in lean and obese could thus shed light on which factors that may be conducive to weight gain. Conversely, lack of observed differences in acute energy intake in a heterogeneous or lean population, do not mean that high glycemic meals are not a cause of increased acute energy intake in the obese. If future studies show that consumption of high glycemic meals indeed plays a major role in the development of obesity, the probable differences between the lean and the obese in the response to high glycemic meals may provide part of the answer to why some get obese and others do not. As previously mentioned results from medium or longer term intervention studies bear much stronger relevance to what the long term outcome of a low glycemic diet may be. To date no long term[3] study has been conducted. The results from several medium term studies are at hand however.

[3] Long term in this paper is considered as more than 2 years.

Medium term studies (5 weeks to 12 months)

Given the poor long term outcome of energy restricted diets, interventions that induce weight loss when a diet is eaten ad libitum tell more about potential outcome in the long term. To our knowledge, only two studies have evaluated the effects of an ad libitum low glycemic diet vs. other ad libitum interventions. The first one compared the effects of a low- vs. a high glycemic diet during pregnancy[117]. The maternal weight gain was much less in the low glycemic group (11.8 kg vs. 19.7 kg; P<0.01) and the infants born to women in the low glycemic group had lower adiposity (301 grams vs. 402 grams; P<0.01). The second study tested a 5 week low glycemic diet vs. a 5 week high glycemic diet in moderately obese men [118]. While there were no differences in body weight, the low glycemic diet was associated with a decrease in fat mass by about 700 grams (P<0.05), and a tendency of increased lean body mass (P <0.07).

A low glycemic ad libitum diet has also been compared to other energy restricted regimens. The first one was a retrospective, nonrandomized cohort study of children attending an outpatient pediatric obesity program, comparing the effects of a low glycemic diet with those of a conventional reduced-fat diet for about 4 months[119]. Body mass index (-1.53 kg/m2 vs 0.06 kg/m2, P<0.001) and body weight (-2.03 kg vs +1.31 kg, P<0.001) decreased more in the low glycemic group compared with the reduced-fat group. Because this study was retrospective and non-randomized, these results must be viewed as preliminary however. The second and longest study of this type was a 12 months randomized controlled trial[120] consisting of a 6 month intervention and a 6 month follow up. Sixteen obese adolescents were included in the study and were either counselled to follow a conventional reduced fat, mildly energy restricted diet, or an ad libitum low glycemic diet. Although both groups changed the composition of the diet according to what they were prescribed, after 12 months fat

mass had decreased by 3 kg in the low glycemic group and had increased by 1.8 kg in the conventional diet group. This result may indicate that a low glycemic diet causes less hunger and that it is easier to follow. Additionally this implies that a low glycemic diet may facilitate reduced energy intake without subjects making a conscious effort at eating less and, conversely, on a high glycemic diet, energy restriction is made difficult.

The weight reduction per se achieved in the few above mentioned studies do not warrant the use of low glycemic diets for obesity treatment. However, there are other findings from these and other studies which seem to make a low glycemic diet rather promising in obesity treatment. On energy restricted diets a low glycemic diet relative to a high glycemic one causes less spontaneous energy intake after energy restriction has been discontinued[121], REE is better preserved[121] and nitrogen balance is less negative[121]. All these factors indicate that weight loss can be maintained more easily on a low glycemic diet as compared to a high glycemic one. Additionally, in the few studies at hand, there are no indications that the effects on body weight are transient by following a low glycemic diet. After the 6 month intervention in the study by Ebbeling et al, body weight did not increase during the 6 month follow up[120].

Diets that are less palatable than the diet one is used to, are likely to be abandoned in the long term and may explain why subjects eat less than they usually do and therefore loose weight. While this could be a possibility with low glycemic diets, there are no clear indications that the high glycemic diets these were compared to, were evaluated as more or less palatable than the other. Thus, in medium term studies the differences in body weight from baseline in absolute figures may not reflect the true weight loss on a low glycemic diet. However, the differences between the high- and the low glycemic regimen in the above mentioned studies should be considered as real, as all regimens limit snack foods and represent a prudent diet.

Whereas it is not the equivalent of a low glycemic diet, α-glucosidase inhibitors such as acarbose, provide an interesting parallel to the effects of postprandial glycemia on

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body weight. α-glucosidase inhibitors reduce postprandial glycemia[122] by delaying, and partly inhibiting, the absorption of carbohydrate, and generally these agents have a weight stabilizing or mild weight reducing effect in patients with diabetes or impaired glucose tolerance[122]. Few studies however have specifically investigated the effects of α-glucosidase inhibitors on body fat mass, implying that the modest weight losses observed could be confounded by changes in body composition. Furthermore the effects may be different in subjects without reduced glucose tolerance or diabetes.

1.5 A hypothetical model for development of obesity on a high glycemic diet

Based on the above mentioned considerations, a high glycemic diet could be one of the contributing factors in the etiology of obesity. A proposed mechanism for how high glycemic meals could lead to obesity is outlined below (Fig. 4).

Figure 4. *A hypothetical model for the development of obesity on a high glycemic diet.*

High postprandial glucose stimulates high insulin secretion and may induce glucotoxicity, which, together with a high insulin secretion, may lead to insulin resistance which again increases insulin secretion. Insulin secretion can also be further increased due to acute postprandial effects of high glycemic meals: appetite control is diminished, leading in turn to bigger meals and a higher preference for high glycemic foods. These factors lead to cycles of continually exacerbating hypersecretion of insulin. In susceptible individuals, this hyperinsulinemia may shift the adipostat in the brain to higher adiposity levels, because of reduced central relative to peripheral effects of insulin. Additionally, fewer meals may lead to reduced muscle mass[123], which in turn may aggravate insulin resistance[124]. In total, the shift in perceived adiposity level by the brain leads to increased hunger, and long term energy intake which is larger than the amount expended. Thus obesity ensues.

2. Objectives

As discussed above several aspects of the responses to high vs. low postprandial blood glucose need further investigation. One primary aim of this study was to evaluate the effect of two normal lunch meals, with a major difference in their glycemic effect, on serum levels of hormones related to appetite. Leptin, ghrelin and insulin were measured as these three hormones may be important with regard to long term outcome on body weight of different diets, as outlined above. Furthermore we wanted to investigate whether potential differences in these hormones would lead to differences in hunger and food intake. In addition, growth hormone was measured due to its counter regulatory effects on hypoglycaemia, which may be observed after the ingestion of high glycemic meals. More specifically, the research questions of the present study were:

1) Will equienergetic intakes of two lunch meals with equal fat content and energy density, but with a major difference in the carbohydrate source and also differences in other nutrients, have different effects on a) the postprandial blood glucose concentration and b) serum levels of hormones related to appetite: insulin, ghrelin, leptin and growth hormone?

2) Will possible differences under 1) in glycemic effect and hormones be reflected in hunger, as estimated by visual analogic scale (VAS), and food intake, as estimated by the amount eaten in the next meal five hours later?

3. Methods

Subjects

First, we tried to recruit subjects by contacting governmental work sites and by putting up posters at the University of Oslo, but this was to no avail. 11 healthy men between the age of 40 and 71 were then recruited through an advertisement in the local newspaper "Aftenposten Aften". All subjects underwent screening at the Institute of General Practice and Community Medicine at the University of Oslo. At the screening the subjects were informed about possible adverse outcomes of taking part in the study, their right to withdraw from the study without giving a reason, their anonymousness and that the study was as approved by the regional ethics committee. They were also informed in general terms about the purpose of the study. After filling out a form where they accepted the terms of the study, they underwent a glucose tolerance test by drinking 50 grams of glucose in 1.5 dl water. All subjects but one had normal glucose tolerance (one subject had a level of 8.1 mmol/l 2 hrs. after drinking the glucose solution), all subjects were overweight (mean BMI: 32,4 [range: 28,7-37,1]), they had no first degree relatives with diabetes type two and none used any medications. Anthropometrical data are shown in table 3.

Table 3. Anthropometrical data

	Mean	SD	Range	Median
Height (cm)	181,8	5,6	172-190	182
BMI (kg · m^{-2})	32,4	2,4	28,7-37,1	32
Weight (kg)	107,1	9,4	93-121	107
Age (years)	51,9	10,6	41-71	46

Protocol

A crossover study was conducted, consisting of two separate 6 hours admissions, separated by a 1-week wash out period (Figure 5). Subjects were randomly assigned to eat low glycemic or high glycemic test meals, simply by giving the first person on the list the first of the two test days the high glycemic lunch.
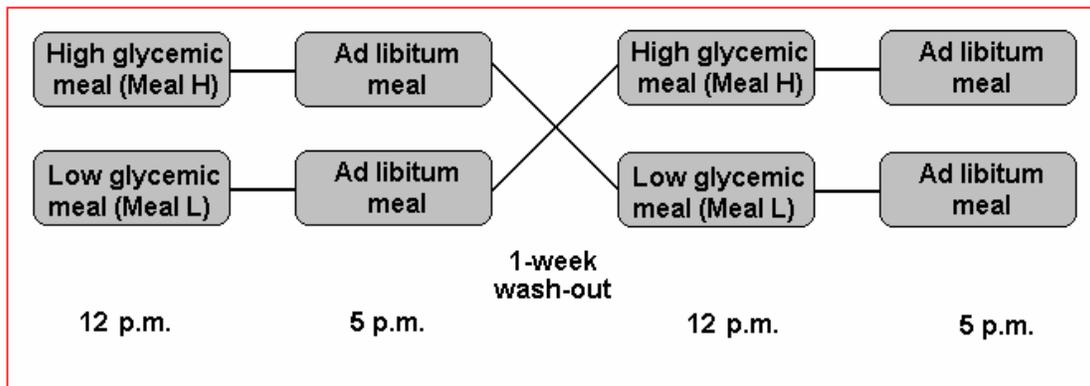

Figure 5. *Study design. Each subject consumed either a low (meal L) or a high glycemic lunch (Meal H) the first day of study and switched to the other lunch the second day of study. At 5 pm both days the subjects ate the same type of ad libitum meal.*

The last two days before the test day, subjects were instructed not to engage in strenuous physical activities and to have a normal diet. At breakfast on the day of the test, a meal consisting of corn flakes and low fat milk was consumed. The amount consumed was the same both test days, and was determined by asking them to pour out an amount of corn flakes and amount of milk that they would usually eat. To ensure that caffeine withdrawal symptoms were avoided, an individually standardized drink for breakfast was consumed both test days. Thus, subjects who normally drink coffee or tea for breakfast did this also on test days. The subjects were instructed to terminate their breakfast before 8.30 a.m.

The subjects were admitted to a hospital research laboratory (Diabeteslaboratoriet, Hormonlaboratoriet, Aker Universitetssykehus) at 11.30 a.m. Each day the subjects

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were asked to fill out a food diary where they reported their food intake the two days preceding the day of the test, and at breakfast the day of the test. Only two subjects were studied per day, one received the high glycemic and the other the low glycemic lunch. The first and the last day of testing for the group as a whole were done within a timeframe of four months. Tuesdays and Thursdays were used as test days. At 11.55 an intravenous line was placed, and the subjects were asked first at 11.58 and then every 30 minutes during 5 hours to record their hunger feeling on VAS. The VAS was a 100 mm line without partition, with at the left end `not at all hungry' (overhodet ikke sulten) and at the other end `extremely hungry' (ekstremt sulten). At 12 p.m. the test meal was consumed. The meal was eaten within 20 minutes. At 12 p.m., and then each half hour blood samples were obtained. During this part of the study, they were allowed to sit down, walk, but not to go out of the laboratory. Between 1 p.m. and 4 p.m. the subjects were allowed to drink a maximum of 400 ml of water, but not more than 200 ml at once. After 5 hours the registration ended and the intravenous line was removed. The subjects then ate a casserole dish ad libitum. The subjects served themselves from a large bowl into a smaller bowl and consumed their meal in an unsupervised fashion. The large bowl was weighed before and after the meal, and the amount consumed was registered. The subjects were instructed to eat until they were comfortably full, but for no longer than 25 minutes. They were not told that their energy intake would be measured at this meal, only that we needed to obtain further data in the satiated state. A blood sample was obtained from a finger for measurement of the blood glucose. This measurement served no other purpose than concealing their food intake being measured. The subjects left the laboratory at 5.30 p.m. At the last day of testing the subjects were asked, using a form (see appendix G), if one of the lunch meals tasted appreciably better than the other, and how good the ad libitum meal tasted.

Test meals

Two isoenergetic lunches (table 4), with different sensory and nutritional characteristics, were composed using combinations of common vegetables, lentils, potatoes and chicken.

Table 4	Meal composition based on a 2735 kJ portion			
	Meal H		Meal L	
Foods	Potatoes	450 g	Lentils	99 g
	Chicken breast	83,3 g	Chicken breast	83,3 g
	Tomatoes	65 g	Onion	200 g
	Broccoli	90 g	Broccoli	250 g
	Olive oil	16 g	Olive oil	14 g
	Spinach	35 g	Water	83 g
	Maizena	18 g		
	Water	40 g		
Fibre		11,8 g		22,3 g
Energy from carbohydrates		55,2 %		41,6 %
Energy from protein		20,4 %		33,9 %
Energy from fat		24,4 %		24,4 %
Energy density		3,2 (kJ/g)		3,2 (kJ/g)
Energy, % of estimated REE		28 %		28 %

The ad libitum meal was a palatable casserole dish consisting of 35% fat, 25 % protein and 40 % carbohydrate (based on energy content).

The Harris Benedict formula [125] was used for the calculation of REE (Resting energy expenditure)(in kJ):

$$REE = 278 + 57,5 \ W + 20.92 \ H - 28,37 \ A$$

W is weight in kilograms; A is age; H is height in centimetres.

Due to the relatively lower metabolic rate of fat mass than that of lean tissue, and the intrinsic limitations of using a formula for this estimation, using this formula does not provide exact values for predicted REE. However, it provided a means to standardize meal size among individuals of different body weight.

Blood analysis

Blood samples were analyzed with the following methods: plasma glucose was measured using a Beckman Glucose Analyzer 2 which determines plasma glucose by means of the oxygen rate method employing a Beckman Oxygen Electrode; serum insulin was measured using a competitive radio immuno assay kit from Linco Research Inc.; serum leptin was measured using a competitive radioimmuno assay kit from Linco Research Inc; serum ghrelin was measured using a competitive radioimmunoassay kit from Linco Research, serum growth hormone was measured using a non-competitive immunofluorumetric assay from AutoDELFIA. All measurements were done in duplicates, and were performed by the staff at the Hormone Laboratory at Aker Hospital.

Data analysis

Hormone and blood glucose concentrations are expressed as mean ± SD. Repeated measures analysis of variance was used to estimate the responses to the meals, using SPSS version 11. Incremental area under the curve values for glucose and insulin were calculated using the trapezoidal rule. For insulin and glucose, their respective p-values refer to differences in IAUC between mean values.

4. Results

Baseline values

At baseline, mean or median serum glucose, insulin, growth hormone, leptin and ghrelin levels were not different between test days H and L (the day meal H and L was consumed, respectively). There were also no differences in reported hunger (Table 5).

	Test day H		Test day L	
	Mean ± SD	Median ± IQR	Mean ± SD	Median ± IQR
Plasma Glucose (mmol/l)	5.6 ± 0.5	5.5 ± 0.6	5.5 ±0.4	5.5 ±0.7
Serum Insulin (pmol/l)	106 ± 42	111 ± 42	91 ±23	89 ± 38
Serum Growth Hormone (µg/l)	0.6 ± 0.7	0.3 ± 0.7	1.1 ± 1.0	0.8 ±1.3
Serum Leptin (pmol/l)	680 ±320	657 ± 227	693 ±275	657 ± 282
Serum Ghrelin (µg/l)	1195 ±256	1077 ± 452	1232 ± 351	1232 ±440
Hunger (cm)	5 ± 2.4	5 ±4.5	5.4 ±2.2	5.8 ± 3.1

Table 5. Baseline levels of glucose, hormones and hunger on the two test days (H and L). Hunger was evaluated using a 10 cm VAS-scale with 'not at all hungry' at the 0 cm end, and 'extremely hungry' at the 10 cm end. Values are expressed as mean ± Standard Deviation (SD), and as median ± Inter Quartile Range (IQR).

Blood glucose concentration

After meal H the glucose level rose to a peak of 8.4 mmol/l at 1 hour and returned to baseline values at approximately 2.5 hours (Fig 6). Thereafter the glucose concentration continued to decline, albeit more slowly, until measurements stopped five hours after the lunch meal. After meal L the glucose response was appreciably less as compared to meal H and rose to a peak of 6.2 mmol/l at 0.5 hours. Glucose levels were lower after meal L as measured by IAUC (104 vs. 249 mmol $\cdot$ l^{-1} $\cdot$ min; P=0.001). After about 2.5 hours glucose levels were the same on both regimens, but thereafter glucose declined more after meal H, being lower relative to meal L from 210 min until measurements stopped at 300 min (P≤0.05). The lowest glucose value observed in an individual was 4.3 mmol/l after meal H (at 150 and 180 min) and 4.8 mmoles/l after meal L (at 120 min). Baseline values were omitted in this comparison.
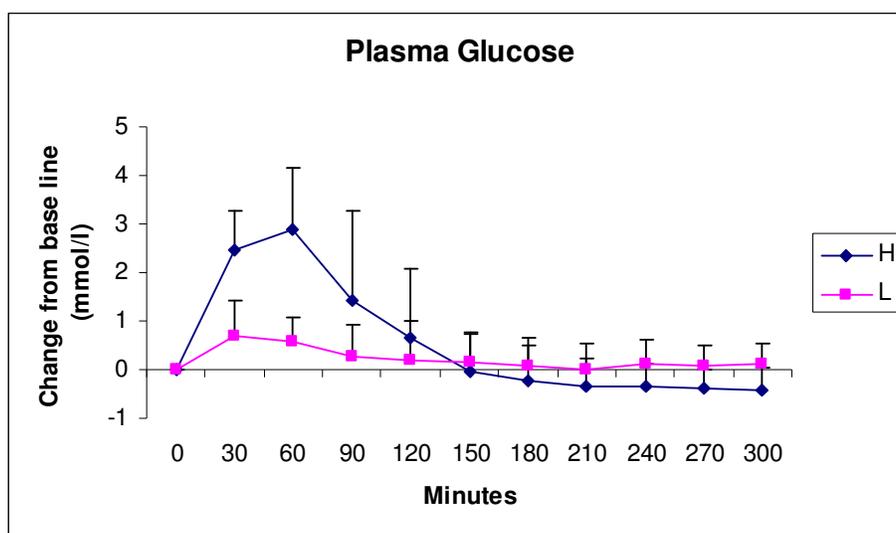

Figure 6. *Changes in plasma glucose levels from baseline after meal H (blue line) and meal L (Pink line) (Mean ± SD, n=11). Baseline values: H=5,6 ± 0.5 mmol/l; L=5.5 ± 0.4 mmol/l (Mean ± SD).*

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Serum insulin concentration

After meal H serum insulin concentration increased to a peak at 1 hour and subsequently declined reaching baseline values after approximately 245 min (Fig. 7). After meal L, the insulin response was blunted, peaked at 1 hour, and declined relatively slowly throughout the remainder of the registration period. The average insulin concentration after meal L did not reach baseline values however. Insulin levels increased appreciably more after meal H as compared with meal L. From baseline, levels increased by 536 pmol/l to peak after meal H and by 137 pmol/l to peak after meal L, and the IAUC was 247 % larger after meal H vs. meal L (58.9 vs. 23.8 pmol/l * min; P=0.007).
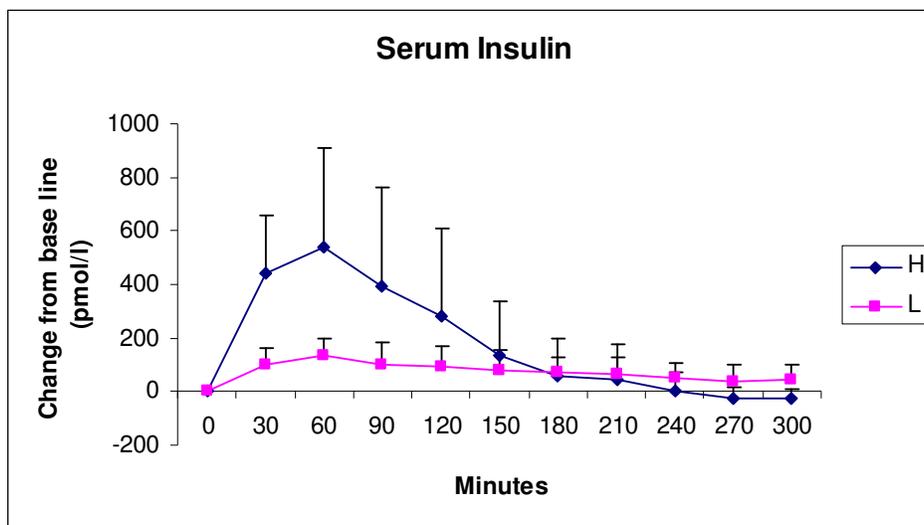

Figure 7. *Changes in serum insulin concentration from baseline after meal H (blue line) and meal L (Pink line) (Mean ± SD, n=11). Baseline values: H=106.4 ± 41.5 pmol/l; L= 91.5 ± 23.1 pmol/l (Mean ± SD).*

Serum growth hormone concentration

After meal H the response curve showed a modest decline during the first hours and thereafter increased to a peak at 240 min (Fig. 8). The shape of the response curve was similar after meal L, but the growth hormone levels did not increase further after returning to baseline levels. The entire curve was lower after meal L relative to meal H. There was a significant time by meal interaction (P=0.036). Growth hormone levels tended to be higher at 270 min (P=0.059) after meal H and was significantly higher at 300 min (P=0.04) (Fig. 8).
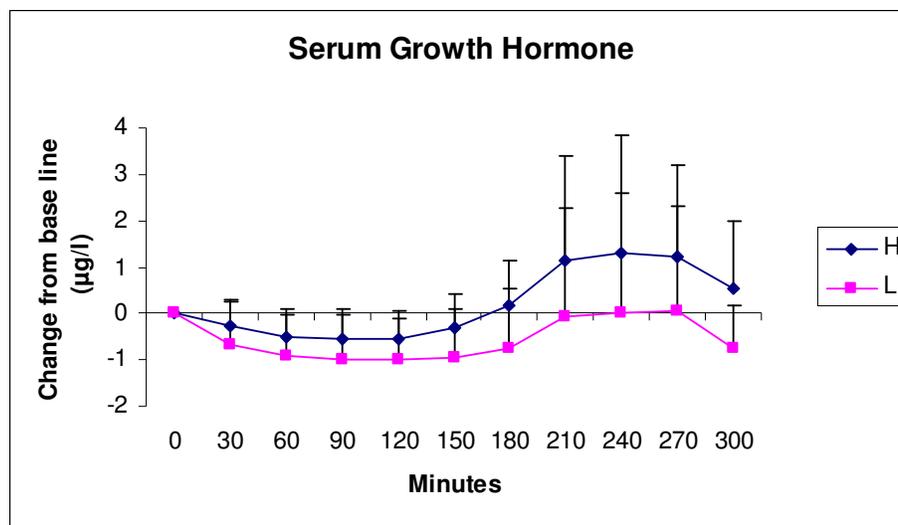

Figure 8. *Changes in serum growth hormone concentration from baseline after meal H (blue line) and meal L (Pink line) (Mean ± SD, n=11). (One sample from one of the subjects is missing.) Baseline values: H=0.62 ± 0.68 µg/l; L=1.12 ± 1.00 µg/l (Mean ± SD).*

Serum leptin concentration

Leptin levels declined during the initial 30 min after meal H and then had, in general, a continuous increase throughout the remaining 4.5 hours of the observation period (Fig 9). After meal L the leptin level reached a nadir at 2 hours and remained approximately at this level the remaining 3 hours. There was a non-significant tendency to higher leptin levels after meal H (P= 0.136) (Fig. 9).
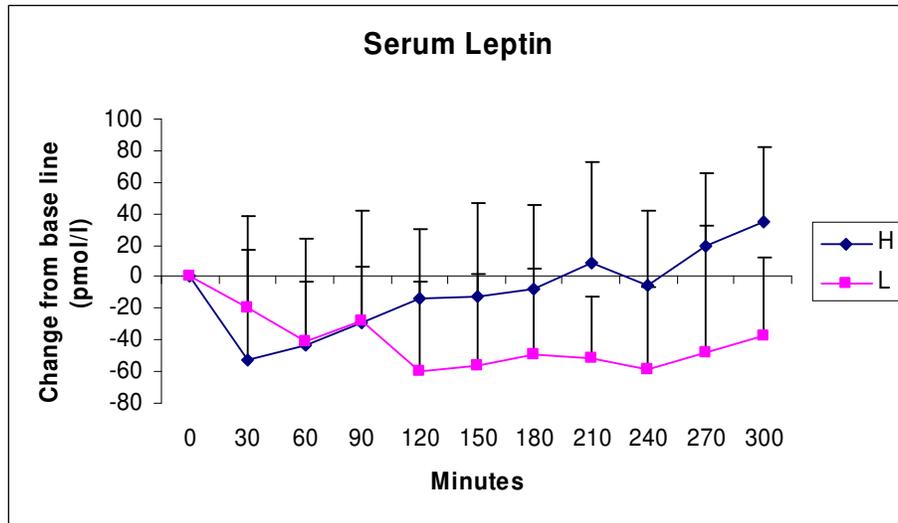

Figure 9. *Changes in serum leptin concentration from baseline after meal H (blue line) and meal L (Pink line) (Mean ± SD, n=11). Baseline values: H=680.3 ± 319.8 pmol/l; L=693.1 ± 274.8 pmol/l (Mean ± SD).*

Serum ghrelin concentration

Whereas ghrelin exhibited a flat curve during the entire 5 hour period after meal L
(Fig 10), the ghrelin response curve was biphasic after meal H, with an initial decline
from baseline at 1 hour, thereafter increasing to a peak at 270 min. There was a
significant time by meal interaction (P= 0.027). Ghrelin levels were lower at 60 min
(P=0.003), and higher at 270 min after meal H (P=0.047) relative to meal L. (Fig. 10).
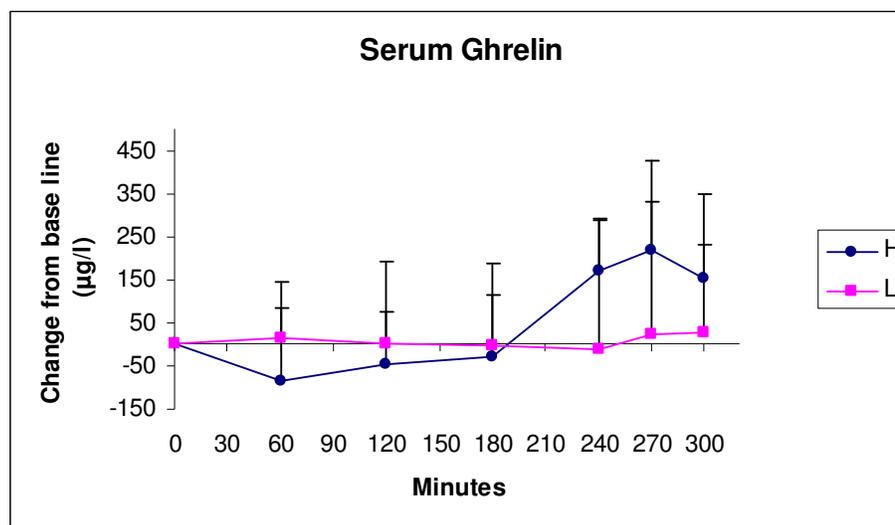
Figure 10. *Changes in serum ghrelin concentrations from baseline after meal H (blue line) and meal L (Pink
line) (Mean ± SD, n=11). (One sample from one of the subjects is missing.) Baseline values: H=1195.0 ± 255.6
µg/l; L=1232.5 ± 350.9 µg/l (Mean ± SD).*

Reported hunger

Reported hunger was lower 30 min after the lunch meal relative to baseline on both regimens (Fig 11). Thereafter hunger increased steadily and reached a peak at the last time of reporting before the 5 pm meal was to be consumed. At no time point was reported hunger different between meal L and H (P=0.985) (Fig. 11).

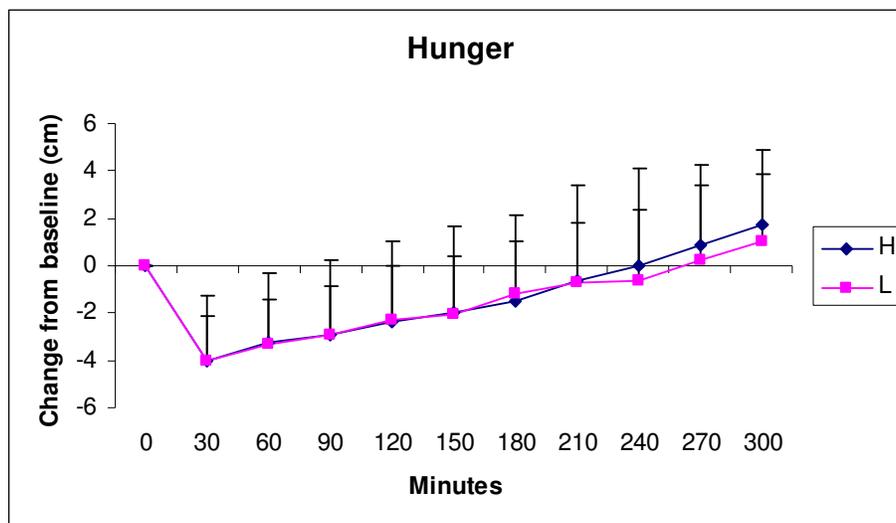**Figure 11.** *Changes from baseline in reported hunger after meal H (blue line) and meal L (Pink line) (Mean ± SD, n=11), as measured by VAS. Baseline values: H=4.97 ± 2.39 cm; L=5.40 ± 2.21 cm (Mean ± SD).*

Energy intake

Energy intake at the second meal was 3665 kJ after the meal H and 3525 after meal L (Fig 12). Differences were not significant between meals (P=0.66).
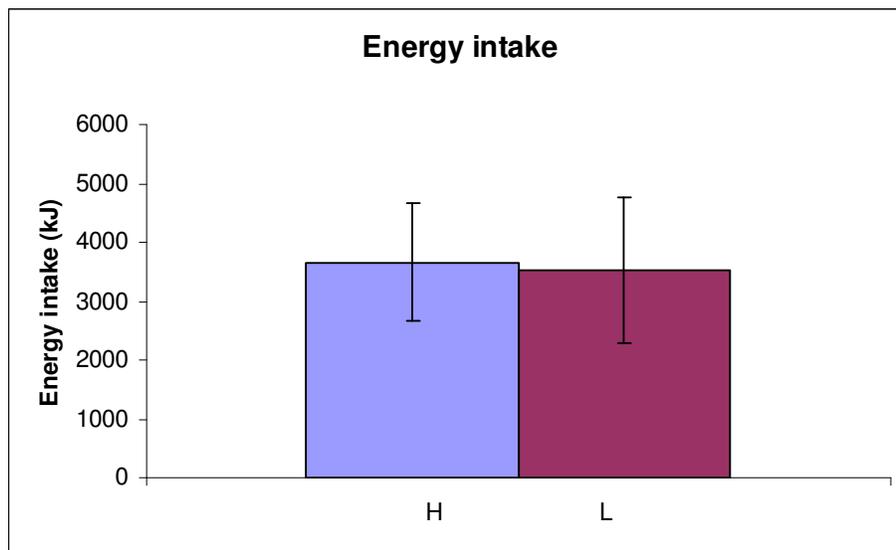
Figure 12. *Energy intake at the 5 p.m. meal after meal H and L (mean ± SD, n=11).*

Correlations

There was a negative correlation between BMI and baseline values of ghrelin (r=-0.727; P=0.011), a positive correlation between BMI and baseline leptin (r=0.748; P=0.008). There were no significant correlations between BMI and glucose (r= -0.242; P=0.474), or BMI and insulin (r=-0.091; P=0.79).

Palatability ratings

Three subjects rated meal L to have appreciably better taste than meal H, while two subjects rated meal H to have appreciably better taste than meal L, and one subject rated meal H to have slightly better taste than meal L. Five subjects did not find that

one meal tasted better than the other. Two subjects found that the ad libitum meal had a taste that was on the poor end (less than 4) on the scale, while nine subjects found that the ad libitum meal had a taste that was on the good end (more than 3) on the scale.

5. Discussion

It would seem from the present study that the research question 1) under "Objectives" (p. 40) can be answered with "yes", whereas question 2) can be answered with "no". Thus, there where differences in hormones known to affect appetite and food intake between meal H and L, but ad libitum food intake was not different on the two regimens, and the hunger scores showed a close concordance between the regimens during the entire five hour period.

Although meals differing in glycemic effect have been questioned with regard to their insulin and glucose responses being different when eaten as the second meal[112], the present study showed that the glucose and insulin responses may differ by more than 100% between two high carbohydrate meals, as measured by IAUC. Additionally, the glucose and insulin levels were remarkably stable after consuming the low glycemic lunch, with only small increases during the observation period. These results indicate that it is possible, simply by choosing another source of carbohydrate, to eat rather large amounts of carbohydrate with only a small subsequent increase in blood glucose. Also, at the end of the observation period there were differences in the level of hormones related to meal initiation and hunger, with levels of ghrelin and growth hormone being larger after the high glycemic meal.

Ghrelin has consistently been shown to be transiently suppressed after meals[55,63,126], but it is unclear what factors related to the meal that induces this effect. In this study, we showed that postprandial ghrelin levels are related to meal composition factors which may include, but also go beyond the gross energy content of the meal. Whereas ghrelin was not different from baseline at any time after meal L, ghrelin showed a biphasic response after meal H. The finding that ghrelin levels under certain circumstances can be unaffected by a meal of normal size is, to the best of our knowledge, new, and may reflect the stability of the overall energy flux after the consumption of a low glycemic meal, by providing a slow and extended time of absorption of nutrients. Also, the fact that ghrelin levels did not increase at the end of

the five hour observation period is somewhat surprising, based on the fact that ghrelin has been shown to increase before all of three meals during the day in a study with a similar meal pattern[63]. These apparent discrepancies may suggest that the type of ingested nutrients, more than time elapsed since the last meal, is a major determinant of ghrelin levels on a short term basis, and that the rise in ghrelin levels, observed at the end of the observation period after the high glycemic meal, in some way may be related to overall energy flux. Possible candidates that may mediate the relation between energy flux and ghrelin levels are insulin and/or glucose, which are observed to have reciprocal 24-h profiles when three normal meals are eaten during the day[63]. Ghrelin levels also had reciprocal profiles with glucose and insulin levels in the present study. It is however not clear whether this pattern is a direct effect, or if it is mediated by other substances such as somatostatin, oxyntomodulin and PYY, which all have been shown to suppress ghrelin levels, and which all increase after meals [57-59]. Although differences in hunger or food intake were not related to changes from baseline ghrelin levels in this postprandial study, potential differences in ghrelin levels after consuming meals differing in glycemic effect may yield different responses on food intake and hunger under other circumstances, or the differences may be of potential long term importance in body weight control due to the orexigenic effects of ghrelin.

Mean leptin levels were not significantly higher different between meal H and L. There are however indications from a previous study[46] that the leptin levels may become significantly different when consuming several meals with different glycemic effects throughout a 24 hour period. Additionally, in a five-week intervention, the expression of the ob-gene was lower on the low glycemic regimen vs. the high glycemic regimen[118]. A lower level of leptin when consuming different diets have been interpreted by some to be an indicator of an increased risk of an increase in body weight[127]. The finding that leptin infusion does not decrease food intake acutely in non-leptin deficient individuals, and that prolonged leptin infusion does not appear to lead to body fat loss in obese humans, questions the role of leptin in body weight regulation in the obese state. Rather, an increase in leptin postprandially seems to be

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primarily mediated by an increased intracellular energy availability in adipocytes[128]. Thus, reductions in leptin levels on a low glycemic diet may indicate that less amounts of nutrients are directed to adipose tissue.

Methodological considerations

There seems to be at least two possible explanations for the similar ad libitum energy intakes and hunger ratings after each of the test meals: 1) there is no difference in hunger or appetite after consuming meal H and L; or 2) hunger ratings and food intake are affected more by external cues than by actual hunger and appetite. It would appear that explanation number 1 does not comprise the entire picture, based on the observed differences in growth hormone, ghrelin and glucose levels at the end of the five hour period. First, the reduction in glucose levels below the fasting values, with concomitant increases in growth hormone, may indicate a perceived reduction in availability of fuels by the body and could thus induce hunger and increased appetite[86]. Second, ghrelin is the strongest systemic, endogenous appetite enhancer known[50]. In this study, postprandial growth hormone and ghrelin levels were higher after the high glycemic meal (after 270 minutes and 300 minutes, for ghrelin and growth hormone respectively), and glucose was lower on the high glycemic regimen during the last two hours of measurement. It is therefore tempting to suggest that reported hunger in this setting could be more regulated by external cues, such as the number of hunger scale forms completed, boredom, time of day etc, than actual hunger. A study by Toumisto et al[129] supports this contention. Similarly, food intake may also have been subject to influence by external cues.

The way of measuring energy intake in this study may not be optimal for the detection of true appetite differences. First, the subjects' energy intake was only recorded at a single meal, which was to be consumed within a limited amount of time. This may have limited the subjects' possibility to "evaluate" if their energy needs were fulfilled. Second, the meal offered at the ad libitum meal was a one choice only. Therefore, subjects were not able to choose between foods that have different properties regarding palatability, energy density, sweetness or other factors that potentially could

have resulted in different energy intakes. Third, subjects were not able to eat when they were hungry and were forced to wait. This may have affected food intake, because in real life situations, food is generally easy accessible. Thus, the ad libitum meal in this study may not reflect the behavioural responses that would most likely occur under free-living conditions. The lack of effect on food intake is in keeping with some studies, and in conflict with others. Of five identified studies comparing mixed meals with differing glycemic effect and their effect on food intake, three[86,130,131] reported a statistically significant result in favour of the low glycemic meal, one[132] reported no difference between meals and one[133] reported a trend in favour of the high glycemic meal. The reasons for the differing results may in part be related to other aspects of the test meals than differences in glycemic effect. Only the study by Ludwig et al[86] appears to have kept possible confounding variables, such as energy density, macronutrient composition, palatability and fibre, constant between meals. When comparing the present study with the study by Ludwig et al[86] however, most of the possible confounding variables in the meals in the present study do not appear to play a significant role with regard to food intake. First, energy density was not different between meals and secondly, palatability was similar in the two meals. Thirdly, the difference in macronutrient composition in this study appears not to be large enough to affect appetite. Specifically, concerning the degree of difference in protein and carbohydrate content in this study, there is support for this not having a significant effect on appetite. In a study by Raben et al[134], where the difference in protein content and carbohydrate was larger between meals than in this study, no effect of protein or carbohydrate on hunger and food intake were observed. One factor which could play a role however, is the amount of available carbohydrate in the two major carbohydrate sources in each of the meals. Lentils consist of a minimum of 10%[135] resistant starch, whereas potatoes consist of around 2%[136] resistant starch (based on total starch). Carbohydrate absorption was therefore probably appreciably less after meal L than after meal H, and could thus have affected hunger ratings and food intake. There are also other, non-meal composition factors, which can explain the discrepancy between the present study and the study by Ludwig et al[86]. One such

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factor could be the age of the subjects. It is possible that children are less affected by external cues than adults when it comes to choosing the amount to eat. Furthermore, the fact that the test meals were given as a second meal of the day in the present study could have affected the outcome. The possible mechanisms involved are not apparent however.

Another factor is the amount of food served, either based on volume or energy content. The energy content of the test meals was 28% of estimated REE, which is larger than the 18.5% REE in the study by Ludwig et al[86]. A few of the subjects that were served the largest amount of food for lunch (i.e. the subjects with the highest estimated REE), complained that the amount of food was larger than what was needed to feel full, and one person informed that he struggled to eat all of the food he was served. This could possibly have affected hunger ratings, and food intake at the ad libitum meal. However, we did not collect information to quantify this aspect in an exact manner. Therefore it is hard to evaluate what effects, if any, this had. It is however possible that the amount of food was so large in this study that the subjects felt overfed on both regimens, and thus the test meals may not reflect normal meal to meal behaviour. Also, ingesting amounts of food which go beyond what is perceived as pleasant, may not reflect usual meal to meal metabolism. In particular, the large amount of food may have overridden the proposed mechanisms in the study by Ludwig et al[86], i.e. that high glycemic meals subsequently render the body in a temporary limited access to metabolic fuels, and thus exacerbate appetite. The mechanism for a potential override effect remains elusive.

Another difference between the study by Ludwig et al[86] and our study is related to specific foods used. The foods most likely to be the more relevant in meal H and L would seem to be lentils and potatoes, as these were the major components of the meals, as measured by weight. Although potatoes yield a relatively high glycemic response, the potato may have other properties which could counteract the effects related to the glycemic response, with regard to hunger and food intake. One such property could be the fibre content. Potatoes contain a considerable amount of fibre,

but it is unlikely that this affected the results, because in other studies, fibre, both fermentable and non-fermentable, has not been shown to have appetite reducing properties [137]. The potato also contains other substances than those mentioned here, but it remains to be investigated what potential effects these substances could have on hunger.

The number of subjects was not large. Thus, the study could have been underpowered with regard to some of the variables. For instance, given the standard deviation observed in this study, a difference of 1880 kJ (53%) at the ad libitum meal would have been needed to detect significant differences.

The subjects' diet and physical activity level during the days prior to study could have affected the results, both due to the fact that the subjects' diet and physical activity level were self reported and the fact that the diet and physical activity instructions were quite general.

One of the subjects informed that he found the intravenous catheter to be very uncomfortable and that thoughts about hunger or eating were rather hard to quantify as his thoughts were appreciably more concerned with the intravenous catheter than with food. A post hoc analysis where this subject was excluded, did not change the results with regard to hunger and food intake.

The difference in glucose and insulin response between the two regimens is larger when evaluated as IAUC than AUC. There are reasons that IAUC was chosen as a measure of insulin and glucose response in this particular study. The major hypothesis was that increments in postprandial blood glucose would set a cascade in motion, as described earlier, which would lead to increased hunger and food intake. Furthermore, low levels of blood glucose are probably most often seen, in non-insulin dependent individuals, after the consumption of foods which give an initial large increment in blood glucose [138]. Thus, if hypoglycaemia is prolonged for a long enough time after hyperglycemia, measuring AUC could nil out the initial hyperglycemia. Similarly, insulin increments bear more relevance to the hypothesis than AUCs, because a high

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level of insulin, rather than a low one, is what is considered important in the regulation of hunger and food intake. Additionally, with regard to other effects of oscillations in blood glucose and insulin within the normal range observed in healthy individuals, high levels of these variables are viewed as more important as causes of pathologic states than are low levels.

This study sought to elucidate one particular mechanism related to obesity development. The inclusion of overweight and obese people in the study which have metabolic derangements as a cause of their high BMI was thus considered important. It does however appear that the classification of overweight and obesity based on BMI may not be the best proxy for the increased health risk associated with higher fat mass, because a large subset of individuals with a BMI over 25 do not have an increased health risk. Thus, their higher than average BMI may be largely set by genetics and less by metabolic derangements.

In general, the reason for the discrepancy between studies on meals with different glycemic effects that have found differences in hunger, and those that have not, need further investigation

Perspectives

As alluded to in the introduction, regulation of body weight is complex. An individual's attempt at interfering with this regulation by eating less than the body demands, i.e. less than what fulfils hunger, is seldom successful in the long term. Thus, the understanding of what factors cause hunger to increase beyond the maintenance of normal body fat stores, is what seems to herald further insights into the etiology of obesity. Recent advancements linked to the discovery of several hormones that affect body weight, body composition, food intake and hunger have increased this understanding, and indicate that a range of factors and systems powerfully act to impede an individual's attempt at reducing body weight. Thus, how these hormones relate to differences in diet, physical activity and other factors, seem to be one area of investigation which may play a major role in the understanding of

obesity development. In this study we have shown that a low glycemic meal relative to a high glycemic one is associated with different short term alterations in the concentration of hormones believed to be central in long term body weight regulation. To what extent these acute differences are significant in long term body weight regulation remains to be further explored.

6. Conclusion

High carbohydrate meals, containing carbohydrates from different sources, can differ greatly in their postprandial glycemic effect, as well as in their influence on hormones known to be involved in appetite regulation. Yet, such differing meals may not influence hunger and food intake, as evaluated by VAS during the next five hours, and by ad libitum food intake at the next meal, in overweight men.

References

1. Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults--The Evidence Report. National Institutes of Health Obes Res 1998;6 Suppl 2:51S-209S.

2. Mokdad AH, Bowman BA, Ford ES, et al. The Continuing Epidemics of Obesity and Diabetes in the United States. JAMA 2001;286:1195.

3. Ebbeling CB, Pawlak DB, Ludwig DS. Childhood obesity: public-health crisis, common sense cure. Lancet 2002;360:473-82.

4. Statens råd for ernæring og fysisk aktivitet. Vekt - helse, rapport nr. 1/2000. Statens Råd for Ernæring og Fysisk Aktivitet 2000.

5. Chan JM, Rimm EB, Colditz GA, Stampfer MJ, Willett WC. Obesity, fat distribution, and weight gain as risk factors for clinical diabetes in men. Diabetes Care 1994;17:961-9.

6. Wadden TA, Sternberg JA, Letizia KA, Stunkard AJ, Foster GD. Treatment of obesity by very low calorie diet, behavior therapy, and their combination: a five-year perspective. Int J Obes 1989;13 Suppl 2:39-46.

7. Krempf M, Louvet JP, Allanic H, et al. Weight reduction and long-term maintenance after 18 months treatment with orlistat for obesity. Int J Obes Relat Metab Disord 2003;27:591-7.

8. Mahan LK, Escott Stump S. Krause's Food, Nutrition, and Diet Therapy. 2000. p.485-515.

9. Bennett WI. Beyond overeating. N Engl J Med 1995;332:673-4.

10. Petersen L, Schnohr P, Sorensen TI. Longitudinal study of the long-term relation between physical activity and obesity in adults. Int J Obes Relat Metab Disord 2003.

11. Weigle DS. Human Obesity - Exploding the Myths. Western Journal of Medicine 1990;153:421-8.

12. Garner DM, Wooley SC. Confronting the Failure of Behavioral and Dietary Treatments for Obesity. Clinical Psychology Review 1991;11:729-80.

13. Donnelly JE, Hill JO, Jacobsen DJ, et al. Effects of a 16-Month Randomized Controlled Exercise Trial on Body Weight and Composition in Young, Overweight Men and Women: The Midwest Exercise Trial. Arch Intern Med 2003;163:1343-50.

14. Fysisk aktivitet og helse -Anbefalinger Statens Råd for Ernæring og Fysisk Aktivitet 2000;Rapport 2.

15. Ludwig DS. Dietary glycemic index and obesity. [Review] [53 refs]. J Nutr 2000;130:280S-3S.

16. No authors listed. Utviklingen i norsk kosthold. Sosial- og Helsedirektoratet 2003.

17. Daily dietary fat and total food-energy intakes--Third National Health and Nutrition Examination Survey, Phase 1, 1988-91 MMWR Morb Mortal Wkly Rep 1994;43:116-5.

18. Schwartz MW, Woods SC, Porte D, Jr., Seeley RJ, Baskin DG. Central nervous system control of food intake. Nature 2000;404:661-71.

19. Cummings DE, Shannon MH. Roles for ghrelin in the regulation of appetite and body weight. Arch Surg 2003;138:389-96.

20. Korner J, Leibel RL. To eat or not to eat - how the gut talks to the brain. N Engl J Med 2003;349:926-8.

21. Halaas JL, Boozer C, Blair-West J, et al. Physiological response to long-term peripheral and central leptin infusion in lean and obese mice. Proc Natl Acad Sci U S A 1997;94:8878-83.

22. Air EL, Benoit SC, Clegg DJ, Seeley RJ, Woods SC. Insulin and leptin combine additively to reduce food intake and body weight in rats. Endocrinology 2002;143:2449-52.

23. Wren AM, Small CJ, Ward HL, et al. The Novel Hypothalamic Peptide Ghrelin Stimulates Food Intake and Growth Hormone Secretion. Endocrinology 2000;141:4325-8.

24. Del Prato S, Leonetti F, Simonson DC, et al. Effect of sustained physiologic hyperinsulinaemia and hyperglycaemia on insulin secretion and insulin sensitivity in man. Diabetologia 1994;37:1025-35.

25. Cusin I, Rohner-Jeanrenaud F, Terrettaz J, Jeanrenaud B. Hyperinsulinemia and its impact on obesity and insulin resistance. Int J Obes Relat Metab Disord 1992;16 Suppl 4:S1-11.

26. Rodin J, Wack J, Ferrannini E, DeFronzo RA. Effect of insulin and glucose on feeding behavior. Metabolism 1985;34:826-31.

27. Velasquez-Mieyer PA, Cowan PA, Arheart KL, et al. Suppression of insulin secretion is associated with weight loss and altered macronutrient intake and preference in a subset of obese adults. International Journal of Obesity 2003;27:219-26.

28. Hoag S, Marshall JA, Jones RH, Hamman RF. High fasting insulin levels associated with lower rates of weight gain in persons with normal glucose tolerance: the San Luis Valley Diabetes Study. Int J Obes Relat Metab Disord 1995;19:175-80.

29. Schwartz MW, Boyko EJ, Kahn SE, Ravussin E, Bogardus C. Reduced insulin secretion: an independent predictor of body weight gain. J Clin Endocrinol Metab 1995;80:1571-6.

30. Swinburn BA, Nyomba BL, Saad MF, et al. Insulin resistance associated with lower rates of weight gain in Pima Indians. J Clin Invest 1991;88:168-73.

31. Valdez R, Mitchell BD, Haffner SM, et al. Predictors of weight change in a bi-ethnic population. The San Antonio Heart Study. Int J Obes Relat Metab Disord 1994;18:85-91.

32. Odeleye OE, de Court, Pettitt DJ, Ravussin E. Fasting hyperinsulinemia is a predictor of increased body weight gain and obesity in Pima Indian children. Diabetes 1997;46:1341-5.

33. Sigal RJ, El Hashimy M, Martin BC, et al. Acute postchallenge hyperinsulinemia predicts weight gain: a prospective study. Diabetes 1997;46:1025-9.

34. Zhang Y, Proenca R, Maffei M, et al. Positional cloning of the mouse obese gene and its human homologue. Nature 1994;372:425-32.

35. Montague CT, Farooqi IS, Whitehead JP, et al. Congenital leptin deficiency is associated with severe early-onset obesity in humans. Nature 1997;387:903-8.

36. Considine RV, Sinha MK, Heiman ML, et al. Serum immunoreactive-leptin concentrations in normal-weight and obese humans. N Engl J Med 1996;334:292-5.

37. Sinha MK, Ohannesian JP, Heiman ML, et al. Nocturnal Rise of Leptin in Lean, Obese, and Non- Insulin-dependent Diabetes Mellitus Subjects. J Clin Invest 1996;97:1344-7.

38. Dallongeville J, Hecquet B, Lebel P, et al. Short term response of circulating leptin to feeding and fasting in man: influence of circadian cycle. Int J Obes Relat Metab Disord 1998;22:728-33.

39. Joannic JL, Oppert JM, Lahlou N, et al. Plasma leptin and hunger ratings in healthy humans. Appetite 1998;30:129-38.

40. Campfield LA, Smith FJ, Guisez Y, Devos R, Burn P. Recombinant mouse OB protein: evidence for a peripheral signal linking adiposity and central neural networks. Science 1995;269:546-9.

41. Pelleymounter MA, Cullen MJ, Baker MB, et al. Effects of the obese gene product on body weight regulation in ob/ob mice. Science 1995;269:540-3.

42. Heymsfield SB, Greenberg AS, Fujioka K, et al. Recombinant leptin for weight loss in obese and lean adults: a randomized, controlled, dose-escalation trial. JAMA 1999;282:1568-75.

43. Hukshorn CJ, Saris WH, Westerterp-Plantenga MS, et al. Weekly subcutaneous pegylated recombinant native human leptin (PEG-OB) administration in obese men. J Clin Endocrinol Metab 2000;85:4003-9.

44. Hukshorn CJ, van Dielen FM, Buurman WA, et al. The effect of pegylated recombinant human leptin (PEG-OB) on weight loss and inflammatory status in obese subjects. Int J Obes Relat Metab Disord 2002;26:504-9.

45. Flier JS. What's in a Name? In Search of Leptin's Physiologic Role. J Clin Endocrinol Metab 1998;83:1407-13.

46. Herrmann TS, Bean ML, Black TM, Wang P, Coleman RA. High glycemic index carbohydrate diet alters the diurnal rhythm of leptin but not insulin concentrations. Exp Biol Med (Maywood) 2001;226:1037-44.

47. Havel PJ, Townsend R, Chaump L, Teff K. High-fat meals reduce 24-h circulating leptin concentrations in women. Diabetes 1999;48:334-41.

48. Evans K, Clark ML, Frayn KN. Carbohydrate and fat have different effects on plasma leptin concentrations and adipose tissue leptin production. Clin Sci (Lond) 2001;100:493-8.

49. Kojima M, Hosoda H, Date Y, et al. Ghrelin is a growth-hormone-releasing acylated peptide from stomach. Nature 1999;402:656-60.

50. Wren AM, Seal LJ, Cohen MA, et al. Ghrelin enhances appetite and increases food intake in humans. Journal of Clinical Endocrinology and Metabolism 2001;86:5992-5.

51. Asakawa A, Inui A, Kaga T, et al. Ghrelin is an appetite-stimulatory signal from stomach with structural resemblance to motilin. Gastroenterology 2001;120:337-45.

52. Tschop M, Smiley DL, Heiman ML. Ghrelin induces adiposity in rodents. Nature 2000;407:908-13.

53. Date Y, Kojima M, Hosoda H, et al. Ghrelin, a novel growth hormone-releasing acylated peptide, is synthesized in a distinct endocrine cell type in the gastrointestinal tracts of rats and humans. Endocrinology 2000;141:4255-61.

54. Tschop M, Weyer C, Tataranni PA, et al. Circulating ghrelin levels are decreased in human obesity. Diabetes 2001;50:707-9.

55. Shiiya T, Nakazato M, Mizuta M, et al. Plasma ghrelin levels in lean and obese humans and the effect of glucose on ghrelin secretion. Journal of Clinical Endocrinology and Metabolism 2002;87:240-4.

56. Nakagawa E, Nagaya N, Okumura H, et al. Hyperglycaemia suppresses the secretion of ghrelin, a novel growth-hormone-releasing peptide: responses to the intravenous and oral administration of glucose. Clin Sci (Lond) 2002;103:325-8.

57. Shimada M, Date Y, Mondal MS, et al. Somatostatin suppresses ghrelin secretion from the rat stomach. Biochem Biophys Res Commun 2003;302:520-5.

58. Cohen MA, Ellis SM, Le Roux CW, et al. Oxyntomodulin suppresses appetite and reduces food intake in humans. J Clin Endocrinol Metab 2003;88:4696-701.

59. Batterham RL, Cohen MA, Ellis SM, et al. Inhibition of Food Intake in Obese Subjects by Peptide YY3-36. N Engl J Med 2003;349:941-8.

60. Broglio F, Gottero C, Benso A, et al. Effects of ghrelin on the insulin and glycemic responses to glucose, arginine, or free fatty acids load in humans. J Clin Endocrinol Metab 2003;88:4268-72.

61. Wren AM, Small CJ, Abbott CR, et al. Ghrelin causes hyperphagia and obesity in rats. Diabetes 2001;50:2540-7.

62. Shuto Y, Shibasaki T, Otagiri A, et al. Hypothalamic growth hormone secretagogue receptor regulates growth hormone secretion, feeding, and adiposity. J Clin Invest 2002;109:1429-36.

63. Cummings DE, Purnell JQ, Frayo RS, et al. A Preprandial Rise in Plasma Ghrelin Levels Suggests a Role in Meal Initiation in Humans. Diabetes 2001;50:1714-9.

64. Wortley KE, Anderson K, Garcia K, et al. Deletion of ghrelin reveals no effect on food intake, but a primary role in energy balance. Obes Res 2004;12:170.

65. English PJ, Ghatei MA, Malik IA, Bloom SR, Wilding JP. Food fails to suppress ghrelin levels in obese humans. J Clin Endocrinol Metab 2002;87:2984.

66. Lee HM, Wang G, Englander EW, Kojima M, Greeley GH, Jr. Ghrelin, A New Gastrointestinal Endocrine Peptide that Stimulates Insulin Secretion: Enteric Distribution, Ontogeny, Influence of Endocrine, and Dietary Manipulations. Endocrinology 2002;143:185-90.

67. Larsen HN, Christensen C, Rasmussen OW, et al. Influence of parboiling and physico-chemical characteristics of rice on the glycaemic index in non-insulin-dependent diabetic subjects. Eur J Clin Nutr 1996;50:22-7.

68. Eschwege E, Richard JL, Thibult N, et al. Coronary heart disease mortality in relation with diabetes, blood glucose and plasma insulin levels. The Paris Prospective Study, ten years later. Horm Metab Res Suppl 1985;15:41-6.

69. Khaw KT, Wareham N, Luben R, et al. Glycated haemoglobin, diabetes, and mortality in men in Norfolk cohort of European Prospective Investigation of Cancer and Nutrition (EPIC-Norfolk). British Medical Journal 2001;322:15-18B.

70. Balkau B. New diagnostic criteria for diabetes and mortality in older adults. DECODE Study Group. European Diabetes Epidemiology Group. Lancet 1999;353:68-9.

71. Coutinho M, Gerstein HC, Wang Y, Yusuf S. The relationship between glucose and incident cardiovascular events. A metaregression analysis of published data from 20 studies of 95,783 individuals followed for 12.4 years. Diabetes Care 1999;22:233-40.

72. Haffner SM, Stern MP, Hazuda HP, Mitchell BD, Patterson JK. Cardiovascular risk factors in confirmed prediabetic individuals. Does the clock for coronary heart disease start ticking before the onset of clinical diabetes? JAMA 1990;263:2893-8.

73. Temelkova-Kurktschiev TS, Koehler C, Henkel E, et al. Postchallenge plasma glucose and glycemic spikes are more strongly associated with atherosclerosis than fasting glucose or HbA1c level. Diabetes Care 2000;23:1830-4.

74. Title LM, Cummings PM, Giddens K, Nassar BA. Oral glucose loading acutely attenuates endothelium-dependent vasodilation in healthy adults without diabetes: an effect prevented by vitamins C and E. Journal of the American College of Cardiology 2000;36:2185-91.

75. Ceriello AF, Bortolotti NF, Motz E FAU - Pieri, et al. Meal-induced oxidative stress and low-density lipoprotein oxidation in diabetes: the possible role of hyperglycemia.

76. Brownlee M, Cerami A, Vlassara H. Advanced glycosylation end products in tissue and the biochemical basis of diabetic complications. N Engl J Med 1988;318:1315-21.

77. Raskin P, Pietri AO, Unger R, Shannon WA, Jr. The effect of diabetic control on the width of skeletal-muscle capillary basement membrane in patients with Type I diabetes mellitus. N Engl J Med 1983;309:1546-50.

78. Rayfield EJ, Ault MJ, Keusch GT, et al. Infection and diabetes: the case for glucose control. Am J Med 1982;72:439-50.

79. Lorenzi M, Montisano DF, Toledo S, Barrieux A. High glucose induces DNA damage in cultured human endothelial cells. J Clin Invest 1986;77:322-5.

80. Lorenzi M, Nordberg JA, Toledo S. High glucose prolongs cell-cycle traversal of cultured human endothelial cells. Diabetes 1987;36:1261-7.

81. Ceriello A, Quagliaro L, D'Amico M, et al. Acute hyperglycemia induces nitrotyrosine formation and apoptosis in perfused heart from rat. Diabetes 2002;51:1076-82.

82. Rossetti L, Giaccari A, DeFronzo RA. Glucose Toxicity. Diabetes Care 1990;13:610-30.

83. Yki-Jarvinen H, Helve E, Koivisto VA. Hyperglycemia decreases glucose uptake in type I diabetes. Diabetes 1987;36:892-6.

84. Garvey WT, Olefsky JM, Marshall S. Insulin receptor down-regulation is linked to an insulin-induced postreceptor defect in the glucose transport system in rat adipocytes. J Clin Invest 1985;76:22-30.

85. Rizza RA, Mandarino LJ, Genest J, Baker BA, Gerich JE. Production of Insulin Resistance by Hyperinsulinemia in Man. Diabetologia 1985;28:70-5.

86. Ludwig DS, Majzoub JA, Al Zahrani A, et al. High glycemic index foods, overeating, and obesity. Pediatrics 1999;103:E26.

87. FAO/WHO. *Carbohydrates in Human Nutrition: Report of a Joint FAO/WHO Expert Consultation,* 14-18 April 1997, Rome. WHO 1998;No. 66.

88. Jenkins DJA, Wolever TMS, Taylor RH, et al. Glycemic Index of Foods - A Physiological-Basis for Carbohydrate Exchange. Am J Clin Nutr 1981;34:362-6.

89. Foster-Powell K, Holt SH, Brand-Miller JC. International table of glycemic index and glycemic load values: 2002. Am J Clin Nutr 2002;76:5-56.

90. Horton TJ, Hill JO. Prolonged fasting significantly changes nutrient oxidation and glucose tolerance after a normal mixed meal. J Appl Physiol 2001;90:155-63.

91. Staub H. Untersuchungen über den Zuckerstoffwechsel des Menschen. Z Klin Med 1921;91:44-8.

92. Traugott K. Über das Verhalten des Blutzuckerspiegels bei wiederholter und verschiedener Art Enteraler Zuckerzufuhr und dessen Bedeutung für die Leberfunktion. Klinische Wochenschrift 3 A.D.;18:892-4.

93. Jenkins DJ, Wolever TM, Taylor RH, et al. Slow release dietary carbohydrate improves second meal tolerance. Am J Clin Nutr 1982;35:1339-46.

94. Wolever TM, Bentum-Williams A, Jenkins DJ. Physiological modulation of plasma free fatty acid concentrations by diet. Metabolic implications in nondiabetic subjects. Diabetes Care 1995;18:962-70.

95. Wolever TM, Jenkins DJ, Ocana AM, Rao VA, Collier GR. Second-meal effect: low-glycemic-index foods eaten at dinner improve subsequent breakfast glycemic response. Am J Clin Nutr 1988;48:1041-7.

96. Bisschop PH, de Metz J, Ackermans MT, et al. Dietary fat content alters insulin-mediated glucose metabolism in healthy men. Am J Clin Nutr 2001;73:554-9.

97. Pruett ED, Oseid S. Effect of exercise on glucose and insulin response to glucose infusion. Scand J Clin Lab Invest 1970;26:277-85.

98. Pruett ED, Maehlum S. Muscular exercise and metabolism in male juvenile diabetics. I. Energy metabolism during exercise. Scand J Clin Lab Invest 1973;32:139-47.

99. Ivy JL, Frishberg BA, Farrell SW, Miller WJ, Sherman WM. Effects of elevated and exercise-reduced muscle glycogen levels on insulin sensitivity. J Appl Physiol 1985;59:154-9.

100. Seim Ekeland G, Beckstrøm AC. Hovedfagsoppgave NIH 2004. Thesis 2004.

101. Basu R, Breda E, Oberg AL, et al. Mechanisms of the age-associated deterioration in glucose tolerance: contribution of alterations in insulin secretion, action, and clearance. Diabetes 2003;52:1738-48.

102. Zimmet PZ, Wall JR, Rome R, Stimmler L, Jarrett RJ. Diurnal variation in glucose tolerance: associated changes in plasma insulin, growth hormone, and non-esterified fatty acids. Br Med J 1974;1:485-8.

103. FAO/WHO. . *Carbohydrates in Human Nutrition: Report of a Joint FAO/WHO Expert Consultation,* 14-18 April 1997, Rome. No. 66. 1998.
Ref Type: Generic

104. Foster-Powell K, Holt SH, Brand-Miller JC. International table of glycemic index and glycemic load values: 2002. Am J Clin Nutr 2002;76:5-56.

105. Wolever TM, Vorster HH, Bjorck I, et al. Determination of the glycaemic index of foods: interlaboratory study. Eur J Clin Nutr 2003;57:475-82.

106. Wolever TM, Jenkins DJ, Vuksan V, et al. Glycemic index of foods in individual subjects. Diabetes Care 1990;13:126-32.

107. Ludwig DS. Glycemic load comes of age. J Nutr 2003;133:2695-6.

108. Coulston AM, Hollenbeck CB, Liu GC, et al. Effect of source of dietary carbohydrate on plasma glucose, insulin, and gastric inhibitory polypeptide responses to test meals in subjects with noninsulin-dependent diabetes mellitus. Am J Clin Nutr 1984;40:965-70.

109. Coulston AM, Hollenbeck CB, Swislocki AL, Reaven GM. Effect of source of dietary carbohydrate on plasma glucose and insulin responses to mixed meals in subjects with NIDDM. Diabetes Care 1987;10:395-400.

110. Wolever TMS, Bolognesi C. Prediction of glucose and insulin responses of normal subjects after consuming mixed meals varying in energy, protein, fat, carbohydrate and glycemic index. J Nutr 1996;126:2807-12.

111. Chew I, Brand JC, Thorburn AW, Truswell AS. Application of glycemic index to mixed meals. Am J Clin Nutr 1988;47:53-6.

112. Pi-Sunyer FX. Glycemic index and disease. Am J Clin Nutr 2002;76:290S-298.

113. Hu FB, Stampfer MJ, Manson JE, et al. Trends in the Incidence of Coronary Heart Disease and Changes in Diet and Lifestyle in Women. N Engl J Med 2000;343:530-7.

114. Raben A. Should obese patients be counselled to follow a low-glycaemic index diet? No. Obesity reviews 2002;3:245-56.

115. Roberts SB. High-glycemic index foods, hunger, and obesity: is there a connection? Nutr Rev 2000;58:163-9.

116. Pawlak DB, Ebbeling CB, Ludwig DS. Spirited critique of glycaemic index (GI) and its role in the treatment of obesity. Obes Rev 2003;4:73-4.

117. Clapp JF. Diet, exercise, and feto-placental growth. Archives of Gynecology and Obstetrics 1997;260:101-8.

118. Bouche C, Rizkalla SW, Luo J, et al. Five-week, low-glycemic index diet decreases total fat mass and improves plasma lipid profile in moderately overweight nondiabetic men. Diabetes Care 2002;25:822-8.

119. Spieth LE, Harnish JD, Lenders CM, et al. A low-glycemic index diet in the treatment of pediatric obesity. Arch Pediatr Adolesc Med 2000;154:947-51.

120. Ebbeling CB, Leidig MM, Sinclair KB, Hangen JP, Ludwig DS. A Reduced-Glycemic Load Diet in the Treatment of Adolescent Obesity. Arch Pediatr Adolesc Med 2003;157:773-9.

121. Agus MS, Swain JF, Larson CL, Eckert EA, Ludwig DS. Dietary composition and physiologic adaptations to energy restriction. Am J Clin Nutr 2000;71:901-7.

122. Scheen AJ. Is there a role for alpha-glucosidase inhibitors in the prevention of type 2 diabetes mellitus? Drugs 2003;63:933-51.

123. Iwao S, Mori K, Sato Y. Effects of meal frequency on body composition during weight control in boxers. Scand J Med Sci Sports 1996;6:265-72.

124. Ivy JL. Role of exercise training in the prevention and treatment of insulin resistance and non-insulin-dependent diabetes mellitus. Sports Med 1997;24:321-36.

125. Harris JA BF. A Biometric Study of Basal Metabolism in Man. 1919.

126. Murakami N, Hayashida T, Kuroiwa T, et al. Role for central ghrelin in food intake and secretion profile of stomach ghrelin in rats. J Endocrinol 2002;174:283-8.

127. Weigle DS FAU - Cummings D, Cummings DE FAU - Newby P, Newby PD FAU - Breen P, et al. Roles of leptin and ghrelin in the loss of body weight caused by a low fat, high carbohydrate diet.

128. Wellhoener P, Fruehwald-Schultes B, Kern W, et al. Glucose metabolism rather than insulin is a main determinant of leptin secretion in humans. J Clin Endocrinol Metab 2000;85:1267-71.

129. TUOMISTO T, TUOMISTO MT, HETHERINGTON M, LAPPALAINEN R. Reasons for Initiation and Cessation of Eating in Obese Men and Women and the Affective Consequences of Eating in Everyday Situations. Appetite 1998;30:211-22.

130. Warren JM, Henry CJ, Simonite V. Low glycemic index breakfasts and reduced food intake in preadolescent children. Pediatrics 2003;112:e414.

131. Holt SH, Delargy HJ, Lawton CL, Blundell JE. The effects of high-carbohydrate vs high-fat breakfasts on feelings of fullness and alertness, and subsequent food intake. Int J Food Sci Nutr 1999;50:13-28.

132. Barkeling B, Rossner S, Sjoberg A. Methodological studies on single meal food intake characteristics in normal weight and obese men and women. Int J Obes Relat Metab Disord 1995;19:284-90.

133. Raben A, Astrup A. Leptin is influenced both by predisposition to obesity and diet composition. Int J Obes Relat Metab Disord 2000;24:450-9.

134. Raben A, Agerholm-Larsen L, Flint A, Holst JJ, Astrup A. Meals with similar energy densities but rich in protein, fat, carbohydrate, or alcohol have different effects on energy expenditure and substrate metabolism but not on appetite and energy intake. Am J Clin Nutr 2003;77:91-100.

135. Tovar J. Bioavailability of carbohydrates in legumes: digestible and indigestible fractions. Arch Latinoam Nutr 1996;44:36S-40S.

136. Liljeberg EH. Resistant starch content in a selection of starchy foods on the Swedish market. Eur J Clin Nutr 2002;56:500-5.

137. Howarth NC, Saltzman E, McCrory MA, et al. Fermentable and nonfermentable fiber supplements did not alter hunger, satiety or body weight in a pilot study of men and women consuming self-selected diets. J Nutr 2003;133:3141-4.

138. Lev-Ran A, Anderson RW. The diagnosis of postprandial hypoglycemia. Diabetes 1981;30:996-9.

7.   Appendices

Appendix A: Ethical committee application

Appendix B: Information to test subjects

Appendix C: Self reported declaration of health status

Appendix D: Diet recommendations two last days before the test day

Appendix E: Pre-test control form

Appendix F: Visual Analogic Scale form

Appendix G: Evaluation of the meals' taste form

Appendix H: E-mail from C. Hukshorn regarding leptin's role in obesity

Appendix A: Ethical committee application

Skjema for etisk vurdering av forskningsprosjekter som vedrører forsøkspersoner/pasienter/klienter/informanter

Søknaden sendes til komiteen i den helseregion hvor prosjektleder har sin arbeidsplass.

Dette skjemaet er tilrettelagt for elektronisk utfylling i MS Word 6.0 eller senere versjoner.

For å gå fra felt til felt i skjemaet benyttes tabulator-tast, mus eller Page Up – Page Down.

Alle felt er dynamiske og utvider seg etter antall linjer som skrives inn. Vennligst skriv i min. 12 pkt. skrift.

Felter med avkrysningsbokser slås på eller av ved å benytte mellomrom-tast eller mus. Ferdig utfylt skjema skrives ut før det signeres av prosjektleder.

Skjemaet lagres på egen PC på samme måte som vanlige Word-dokument. Ved lagring anbefales det å endre dokumentets navn (f.eks. i overensstemmelse med prosjektets tittel).

Alle felt som har relevans for prosjektet skal fylles ut. **Rubrikkene nr. 5, 6, 9, 15 skal besvares**. Prosjektet blir ikke vurdert før disse opplysningene foreligger. Sakspapirer skal ikke innsendes på faks eller som vedlegg til e-post.

Det gjøres oppmerksom på at offentlighetsloven er gjort gjeldende for komiteenes virkomhet fra 1. juli 2001.

1. Tittel

Forskningsprosjektets tittel (kort formulering på norsk) og evt. protokollidentifikasjon:

Glykemisk indeks, blodsukkerregulering og overvekt.

De regionale komiteer for

medisinsk forskningsetikk

2. Prosjektleder

Etternavn, fornavn Høstmark, Arne T.		Akademisk grad/utdanning: dr.med	Stilling: professor
Arbeidssted: Seksjon for forebyggende medisin og epidemiologi, Inst. for allmenn- og samfunnsmedisin, UiO	Adresse: Postboks 1130, 0318 Oslo		E-post: a.t.hostmark@samfunns med.uio.no

Nettside for skjema og veiledning: http://www.etikkom.no/NEM/REK/skjema.doc

Postnr.:	Poststed:	Tlf.:
0318	Oslo	22858284
		Faks:
		22858280

Medarbeidere (navn, tittel, stilling, arbeidssted):

Kåre Birkeland, dr. med, avdelingsoverlege, Endokrinologisk poliklinikk, Aker Sykehus

Ved studentprosjekter oppgis navn på den student som skal gjennomføre prosjektet:

Inge A. Lindseth

Prosjektomfang:

Enkeltinstitusjon ☒

Nasjonal multisenterstudie ☐

Internasjonal multisenterstudie ☐

3. Oppdragsgiver

Fullstendig navn:	Adresse:	Tlf.:
-	-	-
		Faks:
		-
Kontaktperson:	E-post:	
-	-	

4. Prosjektbeskrivelse

Prosjektbeskrivelsen må gis en alminnelig og forståelig språkform på norsk. Det må redegjøres kort for hensikt, hypotese, metode, tidsrom og prinsipper for utvelgelse av forsøkspersoner/informanter og aldersgrupper. Det er ikke tilstrekkelig å henvise til protokoll. Forsøksprotokoll og evt spørreskjemaer etc skal vedlegges.

Introduksjon/problemstilling: Glykemisk indeks er et mål på karbohydratholdige matvarers evne til å øke blodsukkeret. Forskning i løpet av de siste 20 årene har vist at begrepet kan være et nyttig verktøy i behandling og forebygging av livsstilssykdommer, spesielt diabetes og overvekt. Imidlertid kreves det mer forskning og sikrere kunnskap. I Norge har det ikke vært gjort studier på sammenhengen mellom sykelighet og GI. Denne studien tar utgangspunkt i norske forhold og tar sikte på å bidra med ny viten til dette forskningsfeltet.

Inntak av måltider med høy glykemisk indeks gir høy blodsukkerstigning og sterk insulinrespons. Hypotesen er at disse effektene, via til dels uklare mekanismer, fører til økt sultfølelse og overspising.

Med dette som bakgrunn har studien som mål å teste effekten av et høy- vs et lav-glykemisk-indeks-måltid på variabler som har med energiomsetning og energiinntak å gjøre. Mer spesifikt vil det vurderes om et høy-GI-måltid fører til økt frivillig energiinntak 5 timer etter testmåltidet, og om denne eventuelle forskjellen kan forklares ut i fra endringer i blodglukose, insulin og adrenalin.

Studiedesign: 12 overvektige deltar i en crossoverstudie, hvor to måltider med henholdssvis høy og lav GI-mat testes på hver forsøksperson med en ukes mellomrom. De to testmåltidene er gjort så like som mulig med unntak av hovedkarbohydratkilden: I høy-GI-måltidet benyttes poteter, mens det i lav-GI-måltidet benyttes linser. Det legges vekt på at det er to reelle måltider som testes, i betydningen at resultatet er godt overførbart til nordmenns faktiske kosthold. Testmåltidene inntas kl 12, blodprøver tas og sultfølelse registreres umiddelbart før og hver halvtime etter testmåltidet frem til det har gått 5 timer. Et ad libitum måltid inntas 5 timer etter testmåltidet, hvor energiinntak registreres. Det benyttes

venøst kateter for måling av hormoner, og kapillærblod fra fingerrtupp for måling av blodglukose. Forsøkspersonen forlater forsøkslokalet kl 17.45. To og to forsøkspersoner testes på samme dag slik at det totalt blir gjennomført 12 testdager.

Målinger: Glukose i blod, og hormonene: insulin, veksthormon, noradrenalin og adrenalin

Laboratorium/Framdriftsplan/Økonomi etc.: Avdelingsoverlege dr. med. Kåre I. Birkeland stiller Hormonlaboratoriets lokaler på Aker sykehus til disposisjon for gjennomføring av selve forsøket.

Prosjektet ble påbegynt i august 2001. Førsøket gjennomføres oktober 2002 - desember 2002, og databearbeiding og rapportskriving gjøres våren 2003.

Første forsøksdag er satt til å være 15. oktober, og forsøket vil foregå på tirsdager og torsdager fram til og med 5. desember.

Prinsipper for utvelgelse av forsøkspersoner og aldersgrupper:

Denne typen mateffektstudier burde gjøres for representative grupper av hele befolkningen. Imidlertid er ressursene i dette forsøket begrensede. Dessuten er forskningsfeltet såpass nytt at det gjelder å maksimere så mange faktorer som mulig for å avgjøre om videre forsøk er nødvendig på flere grupper av befolkningen. Det antas at overvektige vil ha de klareste effektene av de ulike måltidene. Da alder kan påvirke en rekke fysiologiske variabler, er aldersspennet begrenset.

5. Vitenskapelig vurdering

Bakgrunn/formål: Nyere forskning tyder på at langvarig økning i mengde blodsukker i de første timene etter matinntak disponerer for utvikling av viktige folkesykdommer/tilstander som fedme, insulinresistens, type-2-diabetes og hjerte- og karsykdommer, men vi har liten kunnskap om i hvilken grad norsk mat med ulik glykemisk indeks påvirker disse helsevariablene. Det er derfor viktig å fremskaffe ny kunnskap om postprandiale responser. Kunnskapen om hvordan forskjellige matvarer påvirker sukkermengden i blodet de nærmeste timene etter et måltid, er dessverre tildels svært mangelfull. Prosjektet tar sikte på å systematisk undersøke postprandiale responser.

Nytte/viktighet: Det er økende dokumentasjon på at høy og langvarig økning i blodsukker etter måltider dosponerer for store folkesykdommer i Norge og andre vestlige land. Studien antas derfor å ha en betydelig nytteverdi fordi den framskaffer kunnskaper som kan hjelpe både den enkelte forbruker, matvareprodusenter og myndighetene når det gjelder valg, tilbud og anbefaling av matvarer.

Valg av metode: Det er nødvendig at studien gjøres på mennesker, pga kvalitative og kvantitaive forskjeller i matresponser mellom mennesker og dyr. Effektmål er sultfølelse, arealet under glukosekurven, frivillig matinntak og insulin- og adrenalinrespons. Disse effektmål er valgt pga at høye postprandiale blodsukkerverdier har vist seg å være assosiert med sykdom, og pga at disse effektmål samlet kan gi forklaringer på hvorfor høy glykemisk indeks mat gir eventuell overspising.

Gjennomførbarhet: Prosjektet forutsetter finansiering, forsøkspersoner, laboratoriefasiliteter og vitenskapelig og teknisk ekspertise. Legat for fremme av hygienisk forskning bidrar med økonomisk støtte, dessuten er matvareprodusenten Helios interessert i å støtte prosjektet. Forsøkspersonene vil bli rekruttert fra Statens Vegvesen i Oslo og/eller fra Helios. Laboratoriemetodene er rutine ved de steder de utføres: Aker sykehus og Ullevål sykehus.

STATISTIKK: Effektmål for de nevnte variabler vil være arealet under kurven (AUC), evt. peak, time-to peak (nadir) eller slope. Forskjeller mellom grupper vil estimeres med Students t-test. Antallet forsøkspersoner er bestemt etter gjennomgang av litteratur vedrørende tilsvarende forsøk, da det ikke er tid og ressurser nok til å gjøre en særskilt pilotstudie (hovedfagsoppgave for Inge Lindseth)

6. Inklusjon av begge kjønn

Studier må dimensjoneres slik at det kan gjøres kjønnsspesifikke analyser av resultatene. Dersom ikke begge kjønn inkluderes, må dette begrunnes. Ved inklusjon av fertile kvinner skal det redegjøres for evt bruk av prevensjon og prosedyrer ved uforutsett graviditet. Ved inklusjon av gravide må prosjektleder vurdere og beskrive mulige konsekvenser for kvinnen og for fosteret og redegjøre for hvilken oppfølging som er planlagt.

Kun menn vil bli inkludert i studien, da menstruasjonsyklus kan påvirke resultatene, og det er ikke kapsitet til å gjøre studien på begge kjønn.

7. Klassifisering (hvis aktuelt, kryss av for mer enn én):

Prosjektet er:		*Prosjektet omfatter:*	
		■ Allerede registrerte data	☐
■ Grunnforskning	☒		
■ Klinisk, anvendt forskning	☒	■ Friske personer	☒
■ Bio- og genteknologisk forskning	☐	■ Pasienter/syke	☐
■ Utprøving av medisinsk utstyr	☐	■ Voksne	☒
		■ Barn (under 18 år)	☐
■ Legemiddelutprøving	☐		
Utprøvningsfase: I ☐ II ☐ III ☐ IV ☐		■ Andre umyndige:	
		■ Kun kvinner/piker	☐
■ Samfunnsmed./epidemiol. forskning	☐	■ Kun menn/gutter	☒
■ Psykologisk forskning	☐	■ Innsatte i fengsel	☐
■ (Annen) samfunnsvitensk. forskning	☒	■ Soldater	☐
		■ Minoritetsgrupper	☐
		■ Personer med redusert kompetanse	
Prosjektet er:			
■ Terapeutisk	☐	for informert samtykke	☐
■ Ikke-terapeutisk	☒	■ Fostre	☐
		■ Lik	☐
		■ Kun annet humant materiale	☐
		Hvilken type:	

Begrunn antall forsøkspersoner/informanter. Når det er relevant, gjør rede for styrkeberegning.

Antall: 12. Dette anses som tilstrekkelig ut i fra lignende studier som er gjort. Jamfør særlig referanse nr 4 i prosjektbeskrivelsen.

8. Informasjon

Redegjør for hvordan forsøkspersonene/informantene rekrutteres og gis informasjon om prosjektet, dets formål, eventuelle risiki, rett til å avbryte o.a. (Skriftlig informasjon til forsøkspersoner, evt. annonser, brosjyrer, samt samtykkeerklæring skal vedlegges. Dersom bare muntlig samtykke innhentes, må dette begrunnes særskilt. Dersom forsøkspersonene omfatter mindreårige, umyndige og/eller andre som ikke kan gi bindende samtykke, må det begrunnes hvorfor disse skal inkluderes. Hvis samtykke ikke kan ivaretas, må det gis en utfyllende begrunnelse for hvorfor prosjektet anses etisk forsvarlig å gjennomføre).

Forsøkpersonene rekrutteres gjennom oppslag på arbeidsplass (vedlegg).

9. Etisk vurdering

Blodprøvetaking vil medføre smerter/ubehag, spesielt ved gjentatt taking av kapillærblod fra fingertupp.

Ubehaget vil imidlertid være av kort varighet. Denne typen blodprøvetaking er rutine ved sykehus og anses å innebære liten risiko. Deltakelse i prosjektet kan på den annen side gi verdifull informasjon til den enkelte. Dels får vedkommende greie på eventuelle forhøyete fasteverdier av blodsukker, og får derfor muligheten til å behandle (ved kostomlegging eller medikamenter) sin tilstand. Derved bedres sjansene til å unngå sykdom pga forhøyete verdier. I tillegg får forsøkspersonene vite sin egen matrespons hva angår økning i blodsukker og endringer i ulike hormoner de nærmeste timene etter måltidet (fasteverdien av glukose kan være 'normal', mens postprandial glykemi er forsterket), noe som også kan gi grunnlag for forebyggende tiltak. Noen kan kanskje også oppfatte gratis måltid som en fordel. Forsøkspersonene bidrar dessuten til å frembringe verdifull informasjon for den generelle befolkning, for helsemyndigheter, og for matvareprodusenter.

Om patologiske blodverdier oppdages vil vedkommende bli henvist til sin fastlege for oppfølging. Falske positive og negative funn vil være et problem for forsøkspersonene. Det antas at falske positive og negative funn er sjeldne.

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10. Prosjektleders forhold til forsøkspersonene/informantene

Redegjør for prosjektlederens forhold til forsøkspersonene/informantene (f.eks. lege/pasient, lærer/student, overordnet/underordnet)

Prosjektlederen er professor ved Universitetet i Oslo. Forsøkspersoner rekrutteres fra instanser som ikke har direkte tilknytning til UiO.

11. Legemiddelutprøving

- Redegjør for utførte og planlagte studier og for hvor mange pasienter som er inkludert i tidligere faser av utprøvingen
- Grunngi dosevalg av studiepreparatet
- Grunngi valg av sammenligningspreparat og dosering av dette i forhold til studiepreparatet. Hvis sammenligningspreparatet er et annet enn standard behandling, må det begrunnes særskilt.
- Grunngi evt. hvorfor pasienter må tas av velregulert behandling
- Grunngi bruk av placebo

12. Risiko

- Redegjør for risiki, som f.eks. smerter, ubehag, psykiske påkjenninger, uhell, komplikasjoner, og for tiltak for å minske/forebygge disse.
- Redegjør for om metodene er klinisk etablert eller ikke. Hvis de er nye, hvordan har prosjektleder og medarbeidere tilegnet seg klinisk erfaring med dem?
- På hvilket grunnlag er risiko vurdert? (dyreforsøk, pilotstudie, klinisk erfaring, etc.)
- Beskriv hvordan komplikasjoner, bivirkninger, uventede hendelser, nye toksiske funn etc blir registrert

Den blodprøvetaking som benyttes er rutine ved sykehus, og anses å innebære liten risiko. Blodprøvetaking vil medføre smerter/ubehag av varierende grad, spesielt ved gjentatt prøvetaking. Hvis forsøkspersonen inviteres til å komme igjen flere ganger, vil vi vanligvis la det gå ca en måned mellom hvert forsøk. Inntak av selve måltidet antas ikke å medføre ubehag. Om så viser seg å bli tilfellet, kan forsøkspersonen trekke seg, ihht samtykkeerklæringen.

13. Forsikring

Forsøkspersonene/informantene er dekket av følgende forsikring ved eventuelle uhell eller komplikasjoner:

Pasientskadeerstatningsordningen	☒	Særskilt forsikring	☐	
Produktansvarsloven	☐	Forsikring ikke aktuelt	☐	(må begrunnes)

14. Beredskap

Redegjør for beredskap for oppfølging dersom grunnlaget for studien endres underveis, så som ved økt risiko, uventede hendelser, nye og/eller mer alvorlige bivirkninger. Drøft evt. behovet for interimsanalyse og mulige tiltak, så som bruk av stoppgruppe, endring av design, endret informasjon til pasienter etc.

Henvisning til fastlege dersom det oppdages patologiske verdier.

15. Honorering av forsøkspersoner/informanter og prosjektleder/medarbeidere

Redegjør for eventuell honorering/kompensasjon for forsøkspersonene/informantene

Hver forsøksperson vil få en godtgjørelse på 200 kr, samt dekning av reiseutgifter. Dessuten blir alle forsøkspersoner tilbudt en gratis kostholdsrelatert helsesjekk

Redegjør for økonomiske ytelser til prosjektleder og medarbeidere fra farmasøytisk industri eller utstyrsleverandører i forbindelse med planlegging og gjennomføring av prosjektet. Redegjør også for evt interessekonflikter for prosjektleder.

Det er søkt om støtte fra Helios, som er en matvareprodusent.

16. Vurdering/godkjenning av andre instanser

Komiteen minner om at noen prosjekter også skal vurderes/godkjennes av eller meldes til andre instanser (evt. uttalelser vedlegges eller ettersendes):

	Er søkt/meldt	Er vurdert/godkjent av	Er ikke aktuelt
- Statens legemiddelverk	☐	☐	☒
- Datatilsynet	☐	☐	☒
- Norsk samfunnsvitenskapelig datatjeneste	☐	☐	☒
- Sosial- og helsedepartementet	☐	☐	☒
- Statens helsetilsyn	☐	☐	☒
- Andre:	☐	☐	☒

17. Publisering og sluttrapport

Vil prosjektleder publisere eller gjøre allment tilgjengelig negative så vel som positive resultater, i henhold til Helsinkideklarasjon? Dersom svaret er nei, må dette begrunnes særskilt.

Resultatene vil søkes offentliggjort etter beste evne. Et ønske er å få resultatene publisert i American Journal of Clinical Nutrition.

Forplikter prosjektleder seg til å sende inn melding til Regional komité for medisinsk forskningsetikk når prosjektet er avsluttet eller når det ikke blir sluttført? Ved legemiddelutprøvinger er det tilstrekkelig at sluttrapport sendes Statens legemiddelverk.

ja

Det forutsettes at et prosjekt forelegges komitéen på nytt, dersom det:

A) under gjennomføringen oppstår uforutsette komplikasjoner,
B) blir gjennomført endringer i de forutsetninger som komitéen har basert sin avgjørelse på, f.eks. skifte av prosjektleder.

Underskrift

Sted:	Dato:
Prosjektleders underskrift:	

Appendix B: Information to test subjects

Kan du tenke deg å delta i et matforsøk for å finne ut mer om hvordan sukker og hormoner i blodet øker de nærmeste timene etter ulike typer måltider? Og hvordan dette påvirker matinntaket?

Vi ønsker å vite mer om dette fordi nyere forskning tyder på at sterk økning i blodsukker i de første timene etter matinntak kan disponere for utvikling av fedme, sukkersyke og hjerte- og karsykdommer. Måltidseffekten kan variere fra en person til en annen, og bero på hvor mye vi spiser, type mat og tilberedning. Prosjektet tar sikte på å undersøke i hvilken grad inntak av forskjellige typer mat påvirker sukker- og hormonmengden i blodet de nærmeste timer etter måltidet, og hvordan dette igjen virker inn på matinntaket. Det benyttes vanlige porsjoner av mat beregnet for den alminnelige befolkning.

Du kan melde deg som deltaker dersom du er mann mellom 20 og 70 år og er frisk. Denne gang er vi interessert i å rekruttere overvektige forsøkspersoner. Meld deg gjerne selv om du er i tvil om du vil bli regnet som overvektig eller ikke. Du kan ikke bruke nikotinholdige produkter forsøksdagen og du kan ikke innta alkohol de siste 48 timene før forsøket.

Noen dager før forsøket må du gjennomgå en blodsukkerbelastingstest og svare på spørsmål om din helse. Dette vil ta i overkant av 2 timer.

Selve forsøket:

Prosjektet gjennomføres på Hormonlaboratoriet på Aker Sykehus. Det vil bli gjennomført to testdager per person. Du må møte kl 11.30, og forsøket blir avsluttet kl 17.45. Dagene før testingen må forsøkspersonene ha en 'normal' kost og 'normal' fysisk aktivitet.

Matforsøket foregår slik: To personer møter fastende kl 11.45. Kl 12 inntar de vanlige porsjoner av en lunsjrett i løpet av 20 min. Før matinntak, og hver halvtime i 5 timer tas en bloddråpe fra fingertupp eller øreflipp for måling av blodsukker. Ved de samme tidspunkter gjøres det også hormonmålinger fra venøst blod. Blodprøvene vil bli tatt via innlagt veneflon i armen. Under testingen må ikke forsøkspersonene spise annen mat eller være i sterk fysisk aktivitet, men kan sitte og lese/gjøre arbeid.

Blodprøvene blir tatt av trenet personell.

Ulemper ved deltakelse
Testdagen kan bli lang. Blodprøvetaking kan medføre noe smerter/ubehag, spesielt ved gjentatt taking av blod fra fingertupp/øreflipp. Ved blodprøvetaking i arm kan det eventuelt komme en bloduttredelse som er helt ufarlig.

Du kan når som helst trekke deg fra deltakelse i studien uten å oppgi grunn. Det vil bli gitt en økonomisk kompensasjon på kr 200.- pr person, og reiseutgifter vil bli dekket. Dessuten vil du bli tilbudt en gratis kostholdsrelatert helsesjekk med rådgivning hos ernæringsfysiolog.

Fordeler med å delta i prosjektet:

Deltakelse i prosjektet kan på den annen side gi verdifull informasjon til forsøkspersonen. Dels får du greie på eventuelle forhøyete fasteverdier av blodsukker, og får derfor muligheten til tidlig behandling (ved kostomlegging eller medikamenter). Derved bedres sjansene til å unngå sykdom pga forhøyete sukkerverdier i blodet. I tillegg får du greie på din egen reaksjon mht økning i blodsukker og hormoner de nærmeste timene etter et måltid (fasteverdien av sukker kan være normal, mens mateffekten er forsterket), noe som også kan gi grunnlag for forebyggende tiltak. Forsøkspersonene bidrar dessuten til å fremskaffe generell nyttig informasjon om matens virkninger. Om det oppdages høye blodverdier, vil du bli rådet til å kontakte fastlegen din.

Matforsøket gjennomføres etter at det er tilrådd fra regional etisk komite. Innhentede data om forsøkspersonene, samt resultater av testene, vil bli behandlet konfidensielt. Ved publisering vil resultatene anonymiseres. Forsøkspersonene vil få tilgang til sine egne resultater.

Vennligst undertegn nedenfor dersom du er villig til å være med i matforsøket. Kryss av for hvilken ukedag som passer best for deg.

SAMTYKKE OM DELTAKELSE

Jeg har lest gjennom "Informasjonsskriv til forsøkspersoner" og gjort meg kjent med innholdet. Jeg ønsker å delta og er klar over hva prosjektet innebærer. Prosjektet er frivillig og det er mulig å trekke seg når som helst uten å oppgi årsak.

Navn (blokkbokstaver):_____

Underskrift:_____

For meg passer det best: Tirsdager   _____
                                          Torsdager   _____

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Appendix C: Self reported declaration of health status

Egenerklæring til legen

Navn: _____

Adresse: _____

Tlf.nr.:_____ _____ Mobil tlf. Nr.:_____

Fødselsdato: _____

Initialer:_____

Sivil Status: _____

Utdannelse: _____

Yrke: _____

Sykdom i familien

Forekommer hjerte-karsykdom *(dvs. hjerteinfarkt, brystkrampe, hjerneslag)* eller høyt blodtrykk hos foreldre, søsken besteforeldre eller foreldres søsken oppstått i en alder under 65 år: *(Sett ring rundt)*

Hvis Ja, angi hvem: _____

JA NEI _____

Forekommer ellers noen av andre sykdommer i din familie, *(Sett ring rundt)*

1. Mage-/tarmsykdommer	Mor	Far	Søsken/besteforeldre
2. Allergi/astma/lungesykdom	Mor	Far	Søsken/besteforeldre
3. Nerve eller muskelsykdom	Mor	Far	Søsken/besteforeldre
4. Sukkersyke	Mor	Far	Søsken/besteforeldre
5. Annen sykdom	Mor	Far	Søsken/besteforeldre

Er noen av dine foreldre eller søsken bortgått?   Ja   Nei

Angi i så fall hvem, i hvilken alder og dødsårsak:

_____

_____

Kommentar til punktene/evt. snakk med legen

_____

_____

Livsstil

Røker du?   Ja   Nei   Aldri røkt   Av og til røker   Eks-røker

Bruker du snus?   Ja   Nei

   For røkere: Gjennomsnittlig sigarettforbruk pr dag: _____

For eks-røkere: Hvor mange år hadde du røkt: _____ år. Hva var ditt gjen-
                          nomsnittlige forbruk pr. dag: _____ sigaretter.

Hvor mange kopper kaffe drikker du vanligvis i løpet av en dag? *(Sett ring rundt)*

     0   1-2   2-5   6-10   mer

Hvor mange enheter* med alkohol drikker du vanligvis i løpet av 14 dager
(Angi mengder for to typiske uker i løpet av siste halvår) ? _____ enheter.

     *1 enhet = ½ *(0,33 l)* flaske pils eller 1 glass rødvin eller 1 dram/drink.

Har du i løpet av siste år drevet regelmessig trening/fysisk aktivitet?

     Ja   Nei   Hvis ja, hvor mange ganger pr.uke: _____

Vil du karakterisere din fysiske form som *(Sett ring rundt)*

     Meget god   God   Middels   Dårlig

Helse

Nedenfor nevnes noen vanlige helseplager. *Alle punkt skal besvares.*

0: Ikke plaget   1: Litt plaget   2: En del plaget   3: Alvorlig

		Siste år	Tidligere	Kommentar
1	Forkjølelse			
2	Hoste			
3	Svimmelhet			
4	Hodepine			
5	Bevegelsessyke (bil, fly, båt)			
6	Vondt i nakke			
7	Vondt i rygg			
8	Smerter i armer, skuldre			
9	Dovenhet i armer/ben			
10	Hjertebank, "ekstraslag"			
11	Brystsmerter			
12	Pustevansker			
13	Smerter i bena ved anstrengelser			
14	Sure oppstøt, "halsbrann"			
15	Sug eller svie i magen			
16	Magekatarr			
17	Mageknipe			
18	"Luftplager"			
19	Løs avføring, diaré			
20	Forstoppelse			
21	Hetetokter			
22	Søvnproblemer			
23	Tretthet			
24	Angst			
25	Nedtrykthet, depresjon			
26	Andre plager, hvilke?			
27	Tannsmerter			
28	Andre helseplager			

Har du oppsøkt lege, fått behandling for noen av disse plager? Hvis ja, presiser:

_____

_____

_____

_____

_____

Har du vært innlagt på sykehus?   Ja   Nei

   Hvor mange ganger? _____

   Angi årstall, hva du ble behandlet for, hvilket sykehus og hvor lenge du var der :

Årstall: Behandlet for: Sykehusets navn: Oppholdets varighet

_____   _____   _____   _____

_____   _____   _____   _____

_____   _____   _____   _____

Medikamenter *(skal besvares)*

Har du i kortere eller lengre tid brukt medikamenter *(også naturmedisin)* i løpet av siste året?

          Ja   Nei   Hvis ja, mot hva, og hvilken type og varighet:

          _____

          _____

Bruker du faste medikamenter *(også naturmedisin)* ?

          Ja   Nei   Hvis ja, mot hva, og hvilken type og varighet:

          _____

          _____

Oppsummering:

Gi en kort beskrivelse av din nåværende helsetilstand:

_____

_____

_____

Tilleggsopplysninger:

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

Jeg erklærer herved at jeg har besvart spørsmålene sannferdig og etter beste vitende:

Sted: _____   **Dato:** _____

Underskrift: _____

Appendix D: Diet recommendations two last days before the test day

Vedlegg
Kostholdsanbefaling to dager før forsøksdagen

Forslaget er hentet fra statens ernæringsråd om sammensetning av kost med 60 % av energien fra karbohydrat, 30% fra fett og 10% fra proteiner. Frokost, lunsj og middag anbefales å inneholde lik energimengde mens kveldsmåltidet kan gi noe mindre.

1.Frokost
Kornblandinger, usukret (ikke cornflakes,honnikorn etc.)
Havregrøt, bruk syltetøy og ikke sukker hvis mulig på.
Grovt brød med ost,leverpostei (unngå her sjokoladepålegg,majones)
Juice,melk
Yoghurt
Frukt og bær til å friske opp kornet.
Egg i tillegg kan være fint .

2. Lunsj
Brød som ved frokost, med ost, syltetøy, kjøttpålegg eller leverpostei
Ved varme lunsjer anbefales pasta og risbasert mat
Frukt (alle typer)
Drikke som ved frokost, mye vann dersom det har vært aktivitet på forhånd.

3. Middag
Hovedingrediensene bør bestå av følgende;
Alltid mye poteter,kokt (ikke pommes frites!) Ris kan gi variasjon
Mye grønnsaker (alle typer), salat
Hoveddel bør være; fet fisk (makrell,laks,ørret), pasta, kylling/kalkunkjøtt eller rødt kjøtt (fileter), (ligg unna hamburgere,"junk food",pølser etc).
Vann
Frukt og bær som dessert (Ikke kaker,puddinger etc)

4. Kveldsmat
Som lunsj.
I tillegg til disse måltidene anbefales eventuelle mellom-måltider bestående av yoghurt eller frukt.
Unngå sjokolade etc.

Appendix E: Pre-test control form

Matinntak og fysisk aktivitetsnivå de siste dagene

Navn:

Har du hatt et spesielt kosthold de siste 2 dagene før i dag? Vennligst kryss av for på hvilken måte kostholdet eventuelt har vært spesielt:

Meget fettrike måltider   ja □   nei □

Meget magre måltider   ja □   nei □

Meget lite inntak av karbohydrater   ja □   nei □

Meget stort inntak av karbohydrater   ja □   nei □

Evt. tilleggskommentarer:

Har du spist hele det avtalte frokostmåltidet i dag, inkludert drikke?

 ja □   nei □

Evt. kommentarer:

Har du drevet fysisk trening eller vært meget fysisk aktiv de siste 2 dagene før i dag, og dagen i dag?

ja □   nei □

Evt. kommentarer:

Appendix F: Visual Analogic Scale form

REGISTRERING AV SULTFØLELSE

Angi hvor sulten du er ved å sette et kryss på linjen nedenfor:

_____

Overhodet ikke sulten   Ekstremt sulten

Appendix G: Evaluation of the meals' taste form

VURDERING AV MÅLTIDENES SMAK

Vi er nå interessert i å vite hvordan måltidene du fikk både i dag og forrige forsøksdag smakte.

Vennligst kryss av:

Det ene lunsjmåltidet smakte klart bedre enn det andre:

Uenig　☐　Delvis uenig　☐　Enig　☐

Hvis du svarte enig eller delvis uenig på forrige spørsmål, hvilket måltid smakte best?

Linsemåltidet　☐　Potetmåltidet　☐

På en skala fra 1 til 6, hvor godt smakte måltidet du fikk kl. 17 (begge forsøksdager)? Sett ring rundt det tallet du synes passer best, hvor 6 er meget god smak og 1 er meget dårlig smak.

1　　2　　3　　4　　5　　6

Appendix H: E-mail from C. Hukshorn regarding leptin's role in obesity

Dear Inge Lindseth,

Leptin treatment is virtually abandoned due to the fact
that even a very high dose of this protein (as administrated
in our own studies) fails to induce significant weight loss in obese
individuals (on a mild hypocaloric diet).
In addition, the costs of recombinant leptin are very high at the moment.
In my opinion, leptin in it's current form (as a protein) has no
therapeutical role in the treatment of obesity (see the theory of
Dr. Flier that suggests that leptin resistance was an evolutionary
advantage which is in line with our experimental results).
However, it is possible that a leptin analog might still be used
to treat obesity in the future.

Sincerely,

Chris Hukshorn.

--
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