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Investigations into the Effects of Turmeric, Cinnamon and Green Tea on Glycaemic Control and Liver Enzymes

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Academic thesis which, by due permission of the Faculty of Medicine at Lund University, will be publicly defended on Friday February 20th in lecture theatre Lilla Aulan at Jan Waldenströms gata 5, the Department of Clinical Sciences, Skåne University Hospital, Malmö, Sweden.

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Title and subtitle Investigations into the Effects of Turmeric, Cinnamon and Green Tea on Glycaemic Control and Liver Enzymes

Abstract

Lifestyle changes such as caloric over-consumption and decreased physical activity are causing overweight and obesity, leading to an epidemic increase in type 2 diabetes mellitus (T2DM). Overweight, cardiovascular disease and diabetes are closely linked, and cardiovascular disease is the most important cause of morbidity and mortality among patients with T2DM. Identifying food that can reduce blood glucose and insulin, and increase satiety can help in the prevention and reduction of diabetes and overweight.

The aim of this research was to gain further knowledge of the role of nutritional interventions, in particular, to find functional foods that reduce postprandial blood glucose and insulin levels in order to improve glycaemic control. Satiety was evaluated in one of the studies to gain an understanding of food factors affecting postprandial satiety.

The ingestion of 6 g turmeric increased postprandial serum insulin levels, but did not seem to affect plasma glucose levels or glycaemic index (GI) in healthy subjects. Thus, turmeric may have an effect on insulin secretion. Green tea showed no glucose- or insulin-lowering effects. However, increased satiety and a feeling of fullness were reported by the participants after drinking green tea. The ingestion of 6 g Ceylon cinnamon had no significant effect on glucose level, insulin response, GI or insulinaemic index. The ingestion of 6 g Cassia cinnamon twice a day for 12 weeks had no significant effect on insulin sensitivity, HbA1c, fasting glucose or body mass index. No significant changes were seen in lipids or liver enzymes.

Key words: Green tea, Cinnamon, Glycaemic control, insulin, liver enzymes

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To my beloved family

Contents

Abstract

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Abbreviations

ACE	angiotensin converting enzyme
ADA	American Diabetes Association
ALAT	alanine aminotransferase
ALP	alkaline phosphatase
ASAT	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under the curve
BMI	body mass index
EC	epicatechin
ECG	epicatechin gallate
EGC	epigallocatechin
EGCG	epigallocatechin gallate
GI	glycaemic index
GII	insulinaemic index
GT	gamma glutamyl transferase
HbA1c	haemoglobin A1c
HDL	high-density lipoprotein
HOMA-IR	homeostatic model assessment of insulin resistance
IFG	impaired fasting glucose
IGT	impaired glucose tolerance
IL-6	interleukin-6
IR-β	insulin receptor- β
IRS	insulin receptor substrate
ISI	insulin sensitivity index
LDL	low-density lipoprotein
mDNA	mitochondrial DNA
MetS	the metabolic syndrome

OGTT	oral glucose tolerance test
PK-INR	prothrombin complex- international normalized ratio
PI-3 kinase	phosphatidylinositol-4, 5-bisphosphate 3-kinase
PPAR-γ	peroxisome proliferator-activated receptor-γ
QUICKI	quantitative insulin sensitivity check index
SD	standard deviation
SEM	standard error of mean
SPSS	statistical package for social sciences
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
TNF-α	tumour necrosis factor-α
VAS	visual analogue scale
WHO	World Health Organization

List of Publications

This thesis is based on the following papers, which will be referred to in the text by their Roman numerals. The papers are appended at the end of this thesis.

I Effects of *Curcuma longa* (turmeric) on postprandial plasma glucose and insulin in healthy subjects. **Wickenberg J**, Ingemansson S L, Hlebowicz J. Nutrition Journal. 2010, 9:43

II Does green tea affect postprandial glucose, insulin and satiety in healthy subjects? A randomized controlled trial. Josic J, Olsson A T, **Wickenberg J**, Lindstedt S, Hlebowicz J. Nutrition Journal. 2010, 9:63

III Ceylon cinnamon does not affect postprandial plasma glucose or insulin in subjects with impaired glucose tolerance. **Wickenberg J**, Lindstedt S, Berntorp K, Nilsson J, Hlebowicz J. British Journal of Nutrition. 2012, 107 (12):1845-9

IV Cassia cinnamon does not change the insulin sensitivity or the liver enzymes in subjects with impaired glucose tolerance. **Wickenberg J**, Lindstedt S, Nilsson J, Hlebowicz J. Nutrition Journal. 2014, 13:96

Introduction

Cardiovascular disease, including coronary heart disease, stroke and peripheral vascular disease, is the most common cause of morbidity and mortality among patients with type 2 diabetes (T2DM). Lifestyle changes, such as caloric over-consumption and decreased physical activity, are causing overweight and obesity, leading to an epidemic increase in T2DM. Over the past three decades, the prevalence of diabetes mellitus worldwide has more than doubled. It has been estimated that the number of people with diabetes worldwide will rise from 6.4% (285 million people) in 2010 to 7.7% (439 million people) by 2030 (1), and the number of obese individuals is projected to rise from 33% (1.3 billion) in 2005 to 57.8% (3.3 billion) in 2030 (2). Diabetes and obesity are two major risk factors for the development of cardiovascular disease, and the above predictions indicate that cardiovascular disease will soon reach epidemic proportions.

Despite decades of research on T2DM, it is still not completely understood why T2DM is one of the major risk factors for coronary heart disease. But it has been hypothesized that both obesity and T2DM increase inflammatory responses, which leads to atherosclerosis. Despite the belief that hyperglycaemia triggers an inflammatory response in the arteries, the relationship between high glucose levels and cardiovascular disease has been studied, but with no apparent threshold (3).

Diets with low glycaemic index (GI) and/or low glycaemic load are associated with a reduced risk of T2DM, comparable to the risk reduction observed with a high intake of dietary fibre and whole-grain products (4, 5). Dietary interventions that reduce blood glucose can thus be expected to reduce the risk of developing T2DM, and thus cardiovascular disease and may, therefore, be of value to public health in general.

Diabetes

Definition and diagnosis

Diabetes mellitus is a metabolic disorder of multiple aetiology, characterized by chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism, resulting from defects in insulin secretion, insulin action, or both (6). There are two main kinds of diabetes, type 1 and 2. Type 1 diabetes (T1DM) is due primarily to autoimmune-mediated destruction of pancreatic-cell islets, resulting in absolute insulin deficiency. People with this kind of diabetes must take exogenous insulin for survival to prevent the development of ketoacidosis. The onset of T1DM is rapid, with classical symptoms, as described below.

The onset of type 2 diabetes (T2DM) is usually slow, with an asymptomatic stage that may last for several years. As glucose levels gradually increase, classic symptoms appear, such as increased thirst (polydipsia), an increased need to urinate (polyuria), increased appetite (polyphagia), weight loss and, to some extent certain infections (7). T2DM usually develops in adulthood and is primarily related to obesity, lack of physical activity, and unhealthy diet. The American Diabetes Association's (ADA) definition of diabetes (both type 1 and type 2) is a single raised glucose level of ≥ 11.1 mmol/l with the above symptoms, *or* raised values of fasting plasma glucose of ≥ 7.0 mmol/l on two occasions, *or* a plasma glucose level of ≥ 11.1 mmol/l following an oral glucose tolerance test (OGTT) using a load of 75 g glucose, two hours after the oral dose, on two occasions (6) (Table 1).

Table 1: American Diabetes Association's definition of diabetes. * Raised values on two occasions

Symptoms of diabetes and a single raised glucose ≥ 11.1 mmol/l
or
Fasting plasma glucose ≥ 7.0 mmol/l on two occasions *
or
Plasma glucose ≥ 11.1 mmol/l after OGTT on two occasions *

Impaired glucose tolerance (IGT) was defined in 1979 by the US National Diabetes Data Group as a state of disturbed glucose metabolism (7). IGT is characterized by intermediate elevations of fasting glucose and/or 2-h glucose values after OGTT to levels higher than in normal subjects, but not as high as in subjects with diabetes. IGT is currently defined by the World Health Organization (WHO) as fasting plasma glucose <7.0 mmol/l and OGTT plasma glucose levels ≥7.8 and <11.1mmol/l (8), 2 h after the OGTT. IGT is associated with muscle insulin resistance and defective insulin secretion, resulting in less efficient disposal of the glucose load during the OGTT (9). IGT is regarded as a transitional stage in the development of T2DM. It is not known whether IGT always precedes diabetes, but it is a strong risk factor.

Impaired fasting glucose (IFG) was defined in 1997 by the ADA as a means of classifying individuals who had fasting glucose levels between those seen in normal subjects and those with diabetes (10). IFG is currently defined by the ADA as a fasting plasma glucose level between 5.6 and 6.9 mmol/l (6), while the definition used by the WHO is a fasting plasma glucose level ≥ 6.1 to 6.9 mmol/l (8).

Prevalence of diabetes type 2

T2DM accounts for around 90% of all diabetes worldwide. The prevalence varies considerably between different populations, from rates above 22% in Saudi Arabia to 5.1% in Cambodia (11). An interesting finding is that the prevalence of diabetes may differ within a population, depending on their living conditions. For example, Japanese descendants living in the USA, have a two- to three-fold higher prevalence of T2DM than the original population in Japan (12). Another example is the Pima Indians in Arizona, whose diet has changed from a traditional indigenous diet to a typical Western diet. They have the highest rate of T2DM in the world (over 50%) (13).

Risk factors

It is well established that certain genetic components, both ethnic and familial, are associated with an increased risk of developing T2DM. For example, the progeny of parent with diabetes will have a 40% chance of developing T2DM, and the relative risk of a sibling of someone with T2DM developing the disease is about 3. When comparing Europeans with Asians who are living in Western countries, it was found that the risk of Asians developing T2DM is two to three times higher than for Europeans (14, 15). The genetics of T2DM is still not fully understood, but the interplay between common genes that influence energy metabolism and the regulation of insulin secretion and the Western lifestyle seems to be the explanation of the predisposition to the disease (15).

The increase in T2DM is thought to be related to changes in lifestyle such as overweight, obesity, diet and decreased physical activity level rather than genetic factors (1).

Obesity and overweight are defined by the WHO as abnormal and excessive fat accumulation that may impair health (16). Overweight results from an energy imbalance between caloric intake and expenditure, both of which are closely related to our social and cultural environment. However, overweight and obesity both have genetic components. The situation is complex, and many genes are involved, but it has been estimated that 25 to 40% of those who are overweight or obese are so because of genetic predisposition (17).Obesity and its association with diabetes has been investigated and confirmed in many studies. However, the distribution

of fat is also important, and abdominal obesity, measured as the waist-to-hip ratio, has been shown to be a strong, independent risk factor for diabetes (18). During recent years, more attention has been focused on the waist circumference, and in some studies the waist circumference has been found to be the most important anthropometric measure of obesity in the prediction of diabetes development (19). However, a recent review found no significant difference between the body mass index (BMI) and circumference measurement (both waist and waist-to-hip) as a risk factor for T2DM independently. Nevertheless compared to other risk factors high BMI and waist circumference were closely associated with T2DM (20). BMI is a simple measure based on an individual's mass and height, and is commonly used to classify overweight and obesity, but also underweight. It is defined as the individual's body mass in kg divided by the square of their height in m. According to the WHO, overweight is defined by a BMI ≥25.00 kg/m^2 and obesity by BMI ≥30.00 kg/m^2.

The prevalence of T2DM increases dramatically with age. According to the US National Health and Nutrition Examination Survey for 2009-2012, 4.3 million US residents aged 20-44 had T2DM, 13.4 million aged 45-64, and 11.2 million aged 65 years or older (21). Age is also a risk factor in populations with higher prevalence of diabetes, such as the Pima Indians in the USA, although the prevalence of T2DM peaks at a lower age, exceeding 50% already at 45-54 years of age (22).

Both cross-sectional and prospective studies have shown a higher prevalence of T2DM in sedentary than in physically active subjects (23-25). In this context, it is also important to consider the possible interactions between degree of physical activity and obesity. Although adjustments were made for degree of obesity in the above-mentioned studies, low physical activity was still an independent risk factor. Dietary habits have long been implicated in the pathogenesis of diabetes. Diets with low GI and low glycaemic load are associated with a reduced risk of T2DM, comparable to the risk reduction observed with a high intake of dietary fibre and whole-grain products (4, 5). However, conflicting results have been reported from studies on the effects of dietary habits, where both fat and carbohydrate intake have been suggested to be the causative factor. In a meta-analysis the different levels of evidence regarding increased and decreased risk of developing diabetes, was compiled. (Table 2).

Table 2. Factors increasing and decreasing the risk of developing diabetes

Increased risk	**Decreased risk**
***Convincing* evidence**	***Convincing* evidence**
• Overweight and obesity	• Voluntary weight loss in the overweight and obese
• Abdominal obesity	• Physical activity
• Physical inactivity	***Presumptive* evidence**
• Maternal diabetes	• Non-starch polysaccharides
***Presumptive* evidence**	***Possible* evidence**
• Saturated fats	• Omega-3 fatty acids
• Intrauterine growth retardation	• Low-GI foods
***Possible* evidence**	• Exclusive breastfeeding for the first 6 months
• Total fat consumption	• Functional foods
• Transfatty acids	

Complications

T2DM is strongly associated with frequent complications of both micro- and macrovascular nature. Chronic hyperglycaemia, which is a feature of diabetes, is associated with long-term damage, dysfunction and failure of different organs, especially the eyes, kidneys, nerves, heart and blood vessels. Microvascular damage causes retinopathy in the eyes, which may cause blindness, and nephropathy in the kidneys, which can lead to renal dysfunction. Peripheral polyneuropathy often causes foot ulcers that may lead to amputation. Autonomic neuropathy leads to gastrointestinal, genitourinary and cardiovascular dysfunction that may give rise to symptoms such as gastroparesis, urinary incontinence, sexual dysfunction and dizziness (11).

Chronic hyperglycaemia also affects the macrovascular system. The central pathological mechanism is atherosclerosis, which leads to cardio-, cerebro- and peripheral vascular symptoms. Subjects with diabetes have a higher risk of myocardial infarction, stroke and cerebrovascular disease, and early intervention is thus important (26).

The Metabolic Syndrome

Definition and diagnosis

In 1988, Reaven coined the term "insulin resistance syndrome", including insulin resistance, hyperinsulinaemia, glucose intolerance (IGT and T2DM), dyslipidaemia and hypertension (27). This is now more commonly referred to as metabolic syndrome (MetS). MetS is a cluster of cardiometabolic risk factors including the above, plus abdominal obesity, proinflammatory and prothrombotic components. In 1998, the WHO proposed a working definition of MetS to encourage research into the problem (11). According to WHO the clinical criteria for MetS is following:

Insulin resistance, identified by one of the following:

- Type 2 diabetes
- Impaired fasting glucose
- Impaired glucose tolerance
- Insulin resistance

Plus any two of the following:

- Antihypertensive medication and/or high blood pressure (≥140 mm Hg systolic or ≥90 mm Hg diastolic)
- Plasma triglycerides ≥1.7 mmol/L
- High-density lipoprotein (HDL) cholesterol <0.9 mmol/L in men or <1.0 mmol/L in women
- BMI >30 kg/m^2 and/or waist:hip ratio >0.9 in men, >0.85 in women
- Urinary albumin excretion rate ≥20 μg/min or albumin:creatinine ratio ≥3.4 mg/mmol

Today there are several definitions of MetS but glucose intolerance or insulin resistance, hypertension, dyslipidaemia and central obesity are always included. Individuals with MetS have an elevated risk of cardiovascular disease, twice that of normal-weight individuals, and a five-fold risk of developing T2DM (28).

Insulin Sensitivity

Insulin resistance

Insulin is a peptide hormone with an anabolic effect. It is produced by beta cells in the pancreas. Among other things, insulin regulates the metabolism of carbohydrates and fats by lipolysis and lipogenesis. It promotes the absorption of glucose from the blood to skeletal muscles and fat tissue, and controls hepatic glucose production, protein turnover and gene expression.

The first study on the concept of insulin resistance was published in 1939 by Himsworth. The results from a modified OGTT showed that the ability of insulin to stimulate glucose uptake varied from person to person. It was concluded that there are at least two types of diabetes, insulin-sensitive and insulin-insensitive (29). Insulin resistance, i.e. low insulin sensitivity, can be defined as a subnormal glucose response to both endogenous and exogenous insulin (30). At the onset of insulin resistance, the pancreas may be able to compensate by the secretion of more insulin. But over time, the beta cells fail to maintain their high rate of insulin production, and insulin deficiency leads to impaired glucose tolerance and eventually overt T2DM. It was thus concluded that the development of non-insulin-dependent diabetes mellitus required two kinds of defects, insulin resistance and impaired insulin secretion (31).

More recently, it has been concluded that the development of insulin resistance is a complicated interaction between genes, lifestyle and various defects in metabolic tissues. Interactions between different tissues start a negative loop that may lead to T2DM. The main consumer of glucose is muscle tissue, and the more resistant the muscle tissue is to insulin, the more insulin the pancreas will have to produce to compensate. Most people with insulin-resistant muscle tissue do not develop T2DM, but remain insulin resistant with normal, or near-normal glucose tolerance (32). Studies has been done to try to explain this phenomena and the speculations of a possible defective gut incretin hormone like glucagon-like peptide 1 in people with T2DM. However, the results have been conflicting and no hard proofs have been concluded (27).

Those with a reduced insulin-mediated uptake of glucose in muscle also exhibit a decrease in insulin mediated inhibition of adipose-tissue lipolysis. The dose-response curves for the action of insulin on muscle and adipose tissue differ considerably from each other, while the degree of insulin resistance in the two tissues is highly correlated (33). A high degree of insulin resistance in both muscle and adipose tissue results in increased plasma insulin and free fatty acid concentrations. This in turn causes increased triglyceride synthesis and secretion in the liver, initiating a cascade of metabolic events. The final result is high triglyceride levels, low levels of high-density lipoproteins (HDL), and high levels of low-density lipoproteins (LDL); a highly atherogenic lipoprotein profile that increases the risk of coronary artery

disease (34). Insulin resistance or impaired glucose tolerance is a key factor in MetS (23) and is thought to be of major importance in the pathogenesis of atherosclerosis (26).

Insulin resistance and its association with essential hypertension may be explained by the reaction of the kidneys to hyperinsulinaemia. To compensate for this hyperinsulinaemia the kidney retains NaCl and water. In addition, the sympathetic nervous system is activated by hyperinsulinaemia which contributes to the association between insulin resistance and essential hypertension (35). Impaired insulin sensitivity is common in obesity and has been recognized to have a close correlation (36-38). However, during recent decades a close relationship has been revealed between metabolism and immunity, and a clear correlation between obesity and chronic inflammation (39). The metabolic and immune systems are closely linked, and a normal inflammatory response also relies on metabolic support. The systems are linked through hormones, cytokines, signalling proteins, bioactive lipids and transcription factors that can play a role in both pathways. Imbalance in the metabolic system affects the immune system, and vice versa. Malnutrition is known to cause immunosuppression, but overnutrition has also been identified as a risk factor for immunoactivation, which leads to diabetes, fatty liver disease, inflammation of the airways and atherosclerosis (40).

Adipose tissue is a dynamic endocrine organ that secretes adipokines, which have both an inflammatory and an immune function. There are many adipokines, but the most studied are interleukin-6 (IL-6), tumour necrosis factor-α (TNF-α), leptin, angiotensinogen and adiponectin. Leptin regulates energy balance and is important in glucose homeostasis. It is produced mainly by adipose tissue, but also by the stomach, the placenta, mammary glands and ovarian follicles. Leptin is regulated, in proportion to fat mass and nutritional status, but also by different hormones, such as TNF-α, glucocorticoids and oestrogen (which increase leptin levels), and free fatty acids, growth hormone and peroxisome proliferator-activated receptor (PPARγ) agonists (which decrease leptin levels). Leptin and insulin act as a feedback loop, in which insulin stimulates leptin secretion and leptin inhibits insulin release (41). Leptin acts as a satiety hormone, suppressing food intake, and can thereby induce weight loss. However, obese individuals have, surprisingly, been found to have enhanced levels of leptin (42). Recent studies have now established leptin resistance in obese patients, indicating that leptin has less effect on satiety in obese than in normal-weight subjects (41, 42).

IL-6 and TNF-α are both elevated in obese individuals, and it is believed that they play a role in insulin sensitivity. TNF-α stimulates leptin, inhibits adiponectin secretion, promotes lipolysis and induces apoptosis of adipocytes. IL-6 may affect the liver and skeletal muscle and induce insulin resistance. Elevated levels of IL-6 are considered a risk factor for the development of diabetes and cardiovascular disease. However, IL-6 may have a completely different effect on the central nervous system, where it regulates appetite, promoting weight loss (41, 43). IL-6 and TNF-α may

decrease insulin sensitivity, but the pathways and the correlation between insulin resistance and inflammation are still unclear.

Adiponectin is believed to be a protective protein with anti-inflammatory and insulin-sensitizing properties. The level of adiponectin is decreased in obese individuals, and in an animal studies a decrease has been seen with the progression of T2DM. Studies have shown conflicting results and the adiponectin pathway is still not known, but it is believed to offer protection against the development of diabetes and cardiovascular disease (41).

The renin-angiotensinogen system and its effect on blood pressure and cardiovascular system are well known. But renin, angiotensinogen, angiotensin, angiotensin-converting enzyme are all produced in adipose tissue, indicating possible chain between adiposity, hypertension, cardiovascular disease and diabetes. The presence of angiotensin-converting enzyme inhibitors has been related to a reduced prevalence of diabetes in different studies, but there are conflicting reports on the effects of the renin-angiotensinogen system on insulin sensitivity (43).

Measurement of insulin sensitivity

Insulin sensitivity has been assessed by several different methods, some of which will be discussed briefly here. In 1979, DeFronzo and colleagues designed a method for measuring insulin sensitivity called the euglycaemic-hyperinsulinaemic clamp (44). This method utilizes the hyperinsulinaemia that is achieved by constant infusion of insulin together with a variable infusion of glucose to maintain plasma glucose at a fixed level. The amount of glucose infused during the last sixty minutes of the test, in relation to the steady-state insulin level, provides a measure of the insulin sensitivity. If high rates of glucose infusion are required (≥7.5 mg/min), the patient is insulin sensitive. Very low levels (≤4.0 mg/min) indicate that the patient is resistant to insulin. Levels between 4.0 and 7.5 mg/min are not definitive and suggest IGT, i.e., the intermediate stage between normal glucose metabolism and T2DM, an early sign of insulin resistance. Advantages of this method are that during the steady-state of euglycaemia the glucose infusion rate is equal to the glucose uptake by all the tissues in the body, the insulin levels are high enough to stimulate peripheral glucose disposal, and the test provides a direct measure of the insulin resistance.

Other methods used to measure insulin resistance include the homeostatic model assessment of insulin resistance (HOMA-IR), the quantitative insulin sensitivity check index (QUICKI) and the insulin sensitivity index (ISI) (45-47). However, these provide indirect measures of insulin resistance. Both HOMA-IR and QUICKI provide quantitative measures based on fasting insulin and fasting glucose levels, while ISI is based on the OGTT. It has been reported that HOMA-IR gives relatively low values in patients with insulin resistance undergoing elective surgery (48) or who have advanced T2DM (49). However, it has been reported in other studies that HOMA-IR shows good correlation with the ISI assessed with the euglycaemic-

hyperinsulinaemic clamp (50). Methods of assessing insulin sensitivity using an OGTT have been proposed in a few studies (51, 52). Although this indirect method of measuring insulin resistance is simple and plays an important role in large-scale studies, the golden standard in smaller studies is the euglycaemic-hyperinsulinaemic clamp.

Satiety and satiation

Satiety and satiation are commonly used interchangeably, but when discussing the regulation of appetite, it is important to make a distinction between them. Satiation is the process that occurs while food is being eaten; it is governed by hormones and stretch receptors in the stomach, and controls the size of a meal. Satiation signals the brain when the meal is over. Satiety, on the other hand, is the state engendered as a consequence of eating, where hunger is suppressed and the urge to consume food is inhibited. Regardless of the energy store in the body, an individual can still long for food, and this is part of appetite regulation. The control of appetite is dependent on many factors, for example, the eating environment, the variety of food items available, age and social situation. The sensation that arises when metabolic signals indicate the need to provide the body with energy through food is referred to as hunger (53).

Obesity is an imbalance between the caloric intake and the energy consumed expended (16). Postprandial satiation and satiety are therefore important in the prevention of obesity (16). The regulation of food intake is complex and involves the gastrointestinal tract, the pancreas, adipose tissue, the central nervous system and adrenal glands. The gastrointestinal tract contains several hormones with different roles. Cholecystokinin is secreted to delay gastric emptying and decreasing gastric acid, which stimulates pancreas to release digestive enzymes. It also stimulates the gall bladder to deliver bile into the small intestine to emulsify fats, aiding the digestion and absorption. Cholecystokinin is believed to causes nausea and induces a satiating effect. The mechanism of suppressed appetite is thought to be both functional and hormonal. Functional by decreasing the gastric emptying rate and hormonally by the vagus nerve which affecting the brain and produce a sensation of satiation. Gastric inhibitory peptide and glucagon-like peptide 1 belongs to a class of molecules referred to as incretins (gastrointestinal hormones). Their main role is to promote insulin release by the pancreas, which is stimulated primarily by hyperosmolarity of glucose in the duodenum. Ghrelin is also a gastrointestinal hormone, secreted by endocrine cells. It is normally released by the empty stomach, and is an indication of hunger, but it has been indicated that ghrelin can be produced in conjunction with high-protein meals. The control of gastric ghrelin production is complex, but stimulation of ghrelin stimulates eating, resulting in weight gain (54). TNFα, IL-6 and IL-1 were first identified as products of the immune system, being produced by macrophages, but it is now indicated that these compounds are

secreted by adipocytes tissue, among others. TNFα and IL-6 are believed to be involved in insulin sensitivity (as discussed above), but paradoxically, they also act on the hypothalamus, reducing appetite. It is also believed that in the major feedback loop involving hypothalamus, to stabilise immune system activity, another effect is loss of appetite and weight loss (54).

Gastric distension plays a role in satiation and satiety (55, 56), but the correlation between gastric distension and satiety has been the subject of discussion (57), and recent data suggest that the reduction in hunger is more likely to be caused by the nutritional composition than gastric distension (56, 58). As discussed earlier leptin and insulin also plays a major part in appetite regulation (54).

Functional Foods

Background

T2DM is a complicated and complex metabolic disorder and the prevalence of diabetes mellitus rising dramatically. Despite aggressive pharmacological interventions, current evidence shows an alarming rise in the occurrence of complications associated with diabetes, such as cardiovascular disease (8).

IGT is a strong risk factor for the development of diabetes. Interventions such as increased exercise and a better diet have shown a significant reduction in the development of T2DM in subjects with IGT (59). T2DM can be prevented or delayed with lifestyle modification and are therefore very important tools for treatment.

The term "functional foods" was first described in Japan in the 1980s, and refers to food containing ingredients that have healthy effects on the body, as well as being nutritious (60). Various types of natural remedies have been used historically for the treatment of ailments, among them cinnamon, turmeric and green tea.

Traditional natural remedies: turmeric, cinnamon and green tea

Cinnamon

The spice cinnamon is obtained from the inner bark of trees from the genus *Cinnamomum*. Ceylon cinnamon, with the botanical name *Cinnamomum zeylanicum/verum* is also known as 'true cinnamon'. However, the related *Cinnamomum cassia/aromataticus, Cinnamomum burmannii* and *Cinnamomum loreirii* are also sold as cinnamon.

Among 49 herbs and spices, Ceylon and Cassia cinnamon were found to be the most effective substances regarding insulin-enhancing biological activity in rat adipocytes (61). A water-soluble polyphenol type-A polymer isolated from *Cinnamomum burmannii* has been shown *in vitro* to enhance the action of insulin by stimulating the insulin receptor kinase and inhibiting the insulin receptor phosphatase, which increases insulin sensitivity (62). In rat adipocytes *in vitro*, cinnamon has been shown to enhance glucose uptake by mimicking the effect of insulin. This potentiates insulin action such as: the insulin-stimulated tyrosine phosphorylation of the insulin receptor, the insulin receptor substrate and its association with phosphatidylinositol 3 kinase (63). When insulin-resistant rats were fed Ceylon cinnamon for 3 weeks their insulin resistance decreased, when measured by the euglycaemic-hyperinsulinaemic clamp, and the explanation given was the improved insulin signalling pathway described above (64). However, in a study on patients with T1DM who were given cinnamon (unknown species), no differences were found in HbA1c, total daily insulin intake, or number of hypoglycaemic episodes, compared with the placebo group (65). This may be explained by the fact that cinnamon decreases insulin resistance, which is not the cause of T1DM.

In 2003, Khan et al. reported remarkable results following the ingestion of 1, 3 and 6 g Cassia cinnamon powder per day for 40 days. Not only were the levels of fasting glucose reduced in subjects with T2DM, but positive effects were also seen on triglyceride, LDL and total cholesterol levels (52). Interest in cinnamon and its effect on patients with T2DM increased after this study, and several others were performed with varying results.

In a previous study on healthy subjects, we found that the ingestion of 6 g Cassia cinnamon powder reduced the postprandial glucose concentration and gastric emptying rate (66). However, no changes were seen in postprandial glucose when healthy subjects ingested 1 g or 3 g Cassia cinnamon (67). This result indicates a

dose-dependent response. In a recently published study, Askari et al. found a reduction in insulin resistance in 23 patients with non-alcoholic fatty liver disease who were given 1.5 g cinnamon (unknown species) per day for 12 weeks (68). Solomon et al. found improved insulin sensitivity in eight healthy men after a 14-day intervention with Cassia cinnamon pills (3 g per day) (69). A reduction in insulin resistance was also seen in six non-diabetic women after the intake of 1 g *Cinnamomun burmannii*, per day in capsules, for 8 weeks (70). In contrast, Vanschoonbeek et al. and Blevins et al. found no difference in fasting glucose levels in T2DM patients after taking 1.5 g Cassia cinnamon per day for 6 weeks, and 1 g Cassia cinnamon per day for 12 weeks, respectively (71, 72).

Insulin resistance plays a key role in the development of diabetes, and cinnamon may have qualities that decrease insulin resistance. However, this has not been verified in humans using direct measurements, i.e. the euglycaemic-hyperinsulinaemic clamp.

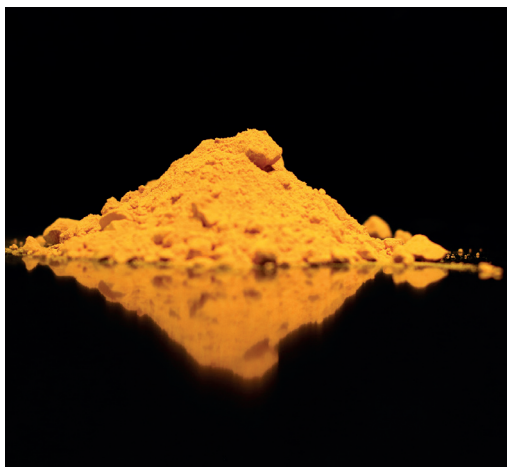
The effects of coumarin

A distinction must be made between Ceylon cinnamon and Cassia cinnamon. Ceylon cinnamon contains hardly any coumarin in contrast to Cassia cinnamon (73). The toxicity of coumarins became the subject of much debate after experimental studies showed hepatotoxicity in dogs (74). The Federal Institute for Risk Assessment in Europe issued a warning on the consumption of cinnamon and established a limit of 0.1 mg coumarin per kg body weight/day. In a study on 114 participants who ingested 30 mg coumarin combined with a vasoactive component, Schmeck-Lindenau et al. found that nine of the patients showed elevated levels of transaminases in serum. But they concluded that the risk of elevated transaminases was limited after risk factors such as a history of hepatitis and other liver diseases were considered (75). Askari et al. reported a reduction in the level of transaminases in 23 patients with non-alcoholic fatty liver disease, who were given 1.5 g cinnamon per day for 12 weeks (68).

Administration of coumarin to diabetic rats indicated alterations in the metabolism of glucose, resulting in a reduction in plasma glucose levels (76, 77). It has also been suggested that coumarin may change the glucose metabolism in healthy rats by reducing the activity of glucose 6-phosphatase in the rat liver, leading to reduced plasma glucose levels (78). The effects of coumarin on glucose and insulin levels in human subjects have not been studied. However, it can be assumed that coumarin ingestion will also affect glucose metabolism in certain ethnicities.

Turmeric

Turmeric, *Curcuma longa*, is a herbaceous perennial plant belonging to the Zingiberaceae family, more widely known as the ginger family. It is native to southeast India, but can also grow in other countries in Southeast Asia. The plant is about 1 m high with elongated leaves and pink flowers, but it is the rhizomes (roots) that are boiled, dried and then ground into a yellow powder. This powder is commonly used as a spice in Asian cooking, but it is also used to colour cheese, butter and yogurt, for example. The active component in turmeric is curcumin, which may constitute 2 to 8% of the spice. The spice is utilized as a traditional medicine in many countries, especially in Asia, and numerous studies have shown that curcumin has antioxidant and anti-inflammatory properties (79).



Both turmeric and curcumin have been extensively studied in animal tests, especially on rats and mice. A study on the effects of ingesting curcumin or turmeric for 3 weeks showed a significant reduction in blood glucose and glycosylated haemoglobin levels (80), as did other studies on the 8-week administration of aqueous turmeric or curcumin to diabetic rats (81, 82). In a study on T2DM mice, the consumption of turmeric in the form of a rhizome extract showed significant increase in blood glucose level. In the same study, the effect on human adipocytes was evaluated, where the extract stimulated adipocyte differentiation, which led to activation of the PPAR-γ (83). PPAR-γ is a key receptor in lipid and glucose homeostasis because of its ability to reduce the free fatty acids in plasma (84). The PPAR-γ pathway is one possible explanation of the antidiabetic effect of turmeric in diabetic mice/rats. Other explanations suggested are that turmeric supresses TNF-α levels and free fatty acids in plasma (85), protects the pancreatic β-cells by inhibition of nuclear factor-κB activation (86), elevates the plasma insulin level, and increases lipoprotein lipase activity (87), all of which increase insulin sensitivity.

Although turmeric has shown remarkable effects on diabetes and its associated complications in animal tests, no clinical trials have yet been reported. A recent review revealed that turmeric has beneficial effects on glycaemic response in animals, but the only clinical trial (including *in vitro* with human cells) using turmeric/curcumin was on the treatment of diabetic nephropathy, microangiopathy and retinopathy (88).

Green tea

Green, yellow, white and black tea are all made from the same plant, *Camellia sinensis,* originally from China. In the wild, this is a tree, but in tea plantations it is trimmed to a shrub with a height of about 1 m. The difference between white, yellow, green and black tea is the processing. The procedure in China involves withering, rolling, oxidizing and drying, while in Japan almost all tea is steamed, thus minimizing oxidation. Because of the steaming procedure, Japan produces mostly green tea. The heat treatment inactivates enzymes in the tea leaves. However, the temperature of pan-drying used in China to make green tea, can reach as high as 230°C, which is much higher than the steaming temperature of 100 °C. Steaming, therefore, results in fewer chemical changes than pan-frying (89).

Tea is the most commonly consumed beverage in the world after water. In recent decades tea has been recognised to have health-promoting properties, including antioxidant activity and anticarcinogenic and antihypertensive effects. Polyphenolic compounds called catechins are thought to be the active components that contribute to these health effects. Green tea contains higher amounts of catechins than black tea, due to the lower temperature of the heat treatment. There are four major catechins in green tea: epicatechin (EC), epicatechin gallate (ECG), epigallocatechin (EGC) and epigallocatechin gallate (EGCG), of which EGCG is the most abundant (90). It has been suggested that green tea may have qualities that affect glucose tolerance, but the results of different studies are conflicting.

Observations of men and women in Japan showed that frequent consumption of green tea was associated with improved glycaemic control and a reduced risk of T2DM (91, 92). EGCG has been shown to be the most effective catechin in the regulation of blood glucose via complex mechanisms involving different pathways *in vitro* and *in vivo*. Examples are the hepatic gluconeogenesis pathway, where

EGCG suppresses gluconeogenesis by decreased expression of gluconeogenic genes (93), insulin-like activity with improved insulin sensitivity (61), and enhancement of insulin sensitivity in adipocytes by increased expression of genes related to insulin sensitivity (94).

Evidence has been found in cross-sectional and cohort animal studies that may support the beneficial effect of green tea on glucose tolerance, but intervention studies on humans have yielded inconsistent results. In a crossover study on 60 patients with IGT, significant improvement in HbA1c levels was seen after the ingestion of 456 mg catechin per day (unknown variety) for 2 months (95). Mozaffari-Khosravi et al. reported a decrease in insulin resistance in T2DM patients after drinking 150 ml green tea three times a day for 4 weeks (96). A significant within-group reduction in insulin resistance and in HbA1c and insulin levels was seen in 35 T2DM patients after the intake of 1500 mg catechin per day (mostly EGCG) for 16 weeks (97). In contrast, Brown et al. and Ryu et al. found no difference in glucose response or insulin sensitivity in 46 men with IGT after taking 800 mg EGCG per day for 8 weeks, or in T2DM patients after drinking 900 ml with 9000 mg green tea per day for 4 weeks, respectively (98, 99). Nagao et al. found no difference in glucose or HbA1c levels in 23 T2DM patients given 582.8 mg catechin supplements per day (a mixture of gallo- and epicatechin) for 12 weeks. However, the insulin level was significantly increased and the waist circumference decreased in the catechin group. An increase in adiponectin level was noted together with a decrease in systolic blood pressure, free fatty acids and total ketone bodies (100).

The Present Investigation

Aims of the Study

The general aim of this thesis was to gain more knowledge on the role of nutritional interventions with regard to insulin sensitivity.

The specific aims of each study are given below:

I To evaluate the effects of turmeric (*Curcuma longa*) on postprandial levels of plasma glucose and insulin, and glycaemic index in healthy subjects

II To investigate whether green tea has any effect on postprandial levels of glucose and insulin, and on glycaemic index or satiety in healthy subjects

III To study the association between Ceylon cinnamon, postprandial plasma glucose and insulin levels, glycaemic index and insulinaemic index in subjects with impaired glucose tolerance

IV To explore the effects of Cassia cinnamon on insulin sensitivity and on liver enzymes in subjects with impaired glucose tolerance

Ethical Committee Approval

The Ethics Committee at the Faculty of Medicine, Lund University approved all four studies (Study I, No. 353/2008), (Study II, No. 353/2008), (Study III, No. 2009/666), (Study IV, No. 353/2008) and all four studies were performed according to the Helsinki Declaration. All subjects gave their written informed consent.

Overview

The following table gives an overview of the studies described in this thesis.

Paper	Design	Subjects	Study duration
I	Randomized, double-blinded crossover trial	14 healthy subjects	August to October 2009
II	Randomized crossover trial	14 healthy subjects	January to February 2010
III	Randomized, double-blinded crossover trial	10 subjects with impaired glucose tolerance	May to September 2009
IV	Randomized, double-blinded, placebo-controlled study	21 subjects with impaired glucose tolerance	August 2011 to Mars 2013

Subjects and Methods

Subjects

The subjects in Studies I and II were healthy students recruited from the population of southern Sweden. Participation was voluntary, and subjects received a small financial reward for their participation. Those who had a history of thyroid disorders or diabetes mellitus type 1 or type 2 were excluded.

The inclusion criterion in Studies III and IV was a diagnosis of IGT in the Malmö Diet and Cancer Study (see below) according to a standard 75 g OGTT, less than 12 months before enrolment. Glucose tolerance status and fasting blood glucose levels were evaluated using the criteria established by the WHO (<7.0 mmol/L and plasma glucose 2 h after OGTT ≥7.8 and <11.1 mmol/L) (8). The exclusion criteria were: thyroid disorders, or taking insulin, oral hypoglycaemics or insulin-sensitizing drugs within 60 days prior to enrolment. Participation was voluntary and without economic compensation.

The Malmö preventive project

The Malmö Diet and Cancer Study was a prospective cohort study, set up to study the association between dietary factors and the incidence of cancer. Participants were recruited from a background population of 74,138 residents, i.e. all the residents of Malmö born between 1923 and 1950 (101). Recruitment was performed between 1991 and 1996 by public advertisement and personal invitation. Participation was voluntary and without economic compensation (102). A prerequisite for eligibility was reading and writing skills in Swedish. The only exclusion criterion was mental incapacity. Of the eligible subjects more then 30,000 (41%) participated (101). Baseline examinations were initiated in 1991 and conducted until 1996. Participants

filled in a questionnaire concerning lifestyle, socioeconomic factors, medication and previous illnesses. Anthropometric measures were made and blood samples taken.

Five years after the baseline examination, all the participants who were still alive were contacted and asked to complete the questionnaire again. More than 22,000 individuals completed the second questionnaire. A follow-up examination was carried out between 2007 and 2012 on over 3,700 individuals. This consisted of a questionnaire, measurements of body constitution, blood pressure an OGTT, ultrasound of the heart and carotid arterial stiffness, and blood sampling.

Methods

Paper I describes a crossover, randomized double-blinded control study. All fourteen healthy volunteers completed the study. Seven were males and seven were females: (mean ± SD) age: 29 ± 1 y (range 25-38 y); BMI: 23.9 ± 2.7 kg/m^2 (range: 20.1-31.5 kg/m^2). The subjects were asked to ingest 15 capsules (described below) containing turmeric or placebo together with 250 mL water within five minutes, after which a standard 75 g OGTT was administered. Samples of blood were taken for laboratory analysis before the meal and then every 15 minutes (as described below).

Paper II describes a crossover randomized control trial without blinding. One of the 15 participants was excluded on the first occasion due to an inability to ingest the food within the required time. The participants thus consisted of seven males and seven females: (mean ± SD) age 27 ± 3 years (range 22-35 years), BMI 22.3 ± 3.4 kg/m^2 (range 17.0-30.8 kg/m^2). The participants were randomized to groups given the test meal or water. The test meal consisted of a total of 50 g carbohydrates served with either 300 mL green tea (green tea meal) or hot water (reference meal). Samples of blood were taken for laboratory analysis before the meal and every 15 minutes after the meal up to 2 hours. The participants reported their subjective assessment of satiety on both occasions (see below).

Paper III describes a crossover randomized control trial with double-blinding. All 10 subjects completed the study: six male and four female: age (mean ± SD) 61 ± 16 years (range 29–73 years); BMI 26.3 ± 4.2 kg/m^2 (range 20.1–32.7 kg/m^2). The participants were given capsules containing placebo or Ceylon cinnamon, after which a standard 75 g OGTT was administered in a random order, at intervals of 1 week. Samples of blood were taken for laboratory analysis before the meal and every 15 minutes after the meal up to 2 hours (see below).

Paper IV describes a randomized, double-blinded placebo-controlled study. By using sealed envelopes the subjects were allocated to the treatment or reference group using stratified randomized selection for age, sex and BMI. The 21 volunteers with IGT were divided into two groups: 10 in the treated group and 11 in the reference group. The participants ingested capsules containing 6 g Cassia cinnamon or placebo, twice a day (i.e. 12 g daily) for 12 weeks. Four subjects dropped out of the study: one for personal reasons (treated group), one had difficulty swallowing

the capsules (reference group), and two had gastrointestinal problems (reference group). During the 12 weeks period, the subjects were examined three times: at baseline, after sex weeks and after 12 weeks. Laboratory analyses were measured at all three times. Anthropometric measurements and insulin sensitivity was measured at baseline and after 12 weeks, in the morning after 12-hour fasting. The changes in insulin resistance were measured using the euglycaemic-hyperinsulinaemic clamp (described below).

Table 5. Clinical and demographic characteristics of the 17 participants in Study IV at baseline

Variable	Treated group	Reference group
Subjects	9	8
Female	5 (56%)	5 (63%)
Men	4 (44%)	3 (37%)
Mean age (years)	73 ± 2	72 ± 2
BMI (kg/m^2)	25.7 ± 1.3	28.6 ± 1.9
Waist circumference (cm)	0.9 ± 0.09	0.9 ± 0.1
Smokers		
No	6 (67%)	8 (100%)
Yes, previously	3 (33%)	0 (0)
Yes, present	0 (0)	0 (0)
Blood pressure		
Systolic	140.5 ± 4.7	122 ± 16.7
Diastolic	82 ± 2.8	80 ± 2.6
Fasting glucose	6.0 ± 0.3	6.7 ±0.4
Fasting insulin	9.8 ± 2.1	11.1 ±2.0
HbA1c	39.6 ± 1.3	40.1 ± 2.4
Total cholesterol	4.9 ± 0.4	4.5 ± 0.2
LDL Cholesterol	3.2 ± 0.4	2.7 ± 0.2
HDL Cholesterol	1.4 ± 0.1	1.5 ± 0.1
Triglycerides	1.1 ± 0.1	1.1 ± 0.1

Anthropometric measurements

All measurements were performed with the subjects in light clothing without shoes. After a minimum of 10 hours overnight fasting the body weight was measured to the nearest 0.1 kg and the height to the nearest cm and the BMI calculated. In Study IV, body weight and height were measured on two separate occasions. Waist and hip circumferences were measured with the subjects standing. The waist circumference was measured at the level of the umbilicus, and the hip circumference at the level of the greater trochanters, with the subjects standing. The waist-to-hip ratio was calculated as a measure of central adiposity.

Substances studied

Turmeric and cinnamon capsules

Turmeric and Ceylon cinnamon powder were purchased from Svampbutiken, Mediapoint AB, Västerås, Sweden. In Studies I and III the capsules were produced by Apoteket, Produktion & Laboratorier, Gothenburg, Sweden. The placebo capsules contained 560 mg lactose, the turmeric capsules (Study I) contained 170 mg lactose and 400 mg *Curcumin longa,* and the cinnamon capsules used in Study III contained 100 mg lactose and 400 mg *Cinnamomum zeylanicum*. To compensate for the differences in the amounts of lactose in the placebo capsules and the turmeric and cinnamon capsules extra lactose was added in the OGTT 15 x 560 mg - 15 x 170 mg = 585 mg, Paper I; and 15 x 560 mg - 15 x 100 mg = 690 mg, Paper III.

All the capsules used in Study IV were prepared by Scandinavian Nutrients AB Strängnäs, Sweden, and contained either 700 mg cellulose (placebo) or 500 mg *Cinnamomum cassia* with 200 mg cellulose.

In Studies I and III a standard 75 g OGTT with lactose was administered directly after the capsules, after a 12-h overnight fast. Capillary blood samples were taken before and during the test to measure blood glucose levels.

Green tea

The test meal consisted of 100 g white bread and 25 g smoked turkey served with either 300 mL green tea (green tea meal) or 300 mL hot water (reference meal). The bread was Skogaholms Originalrost, obtained from Bageri Skogaholm AB, Eskilstuna, Sweden, and contained 50 g carbohydrates, 8 g protein, 3 g fat and 2.5 g dietary fibre. The smoked turkey was from Cascina serena, H. Kemper GmbH & Co. KG, Nortrup, Germany, and contained 4.5 g protein, 0.75 g fat and 0.25 g carbohydrates. The total amount of carbohydrates in the meal was 50 g, as recommended by Brouns et al., in their description of GI methodology (103).

The tea was ordered from Aftek Te & Kryddor AB, Arbrå, Sweden, and was a Japanese Green Sencha Makoto tea. The tea was prepared by brewing 9.00 g of loose-leaf green tea in 300 ml water (initial temperature 80-85°C) for 3 min. The serving temperature of the beverages was 60-65°C. The tea was analysed by ALS Scandinavia AB, Täby, Sweden. The amount of caffeine in the brewed tea was 26.5 mg/100 ml, and the amounts of catechins per 100 ml tea were: EC 8.5 mg, ECG 29.9 mg, EGC <1.0 mg and EGCG 10.8 mg.

Satiety

In Study II a validated visual analogue scale (VAS) was used to assess the participants subjective satiety, based on a scoring system from -10 (extreme hunger) to + 10 (extreme satiety) (104). A more extensive questionnaire was also used for self-reported ratings of different feelings of satiety. The questionnaire was presented in a small booklet showing only one question at a time. The questions asked were: "How hungry are you?" (hereafter denoted "hunger"), "How pleasant would you find eating another mouthful of this food?" ("pleasant"), "How strong is your desire to eat your favourite food at the moment?" ("desire"), "How full do you feel at the moment?" ("fullness"), "How nauseous do you feel at the moment?" ("nausea"), and "How strongly do you feel that you have had enough to eat?" ("enough"). The subjects were asked to rate the different sensations on a 15 cm VAS anchored by the phrases "Not at all" and "Extremely" (105). Hunger, desire, sickness and fullness were estimated before the meal (0 min), and all feelings of satiety were evaluated 15, 30, 45, 60, 90 and 120 min after the start of the meal.

Laboratory analyses

Finger-prick capillary and venous blood samples were taken before and 15, 30, 45, 60, 90, 120, 150 (Studies I and II), and 180 min (Study III) after the start of the meal, to determine glucose and insulin levels. Glucose concentrations were measured with the HemoCue Glucose system (HemoCue AB, Ängelholm, Sweden), which converts blood glucose to plasma-equivalent glucose concentrations by multiplying by a constant factor of 1.11 (106). The precision of the HemoCue Glucose system is better than ± 0.3 SD between 0 and 22.2 mmol/L. All venous blood samples were centrifuged at 3000 × g for 10 min at 4°C. Aliquots of serum were immediately stored at -25°C for later analysis. Insulin concentrations were measured using an immunoassay with an alkaline phosphatase conjugate (Access Ultrasensitive Insulin, Beckman-Coulter AB, Bromma, Sweden). The sensitivity of the insulin immunoassay was 0.03 mUnit/L (mU/L) and the intra-assay coefficient of variation was less than10% in the interval 0.03 to 300 mU/L.

In Study IV, all analyses of plasma and whole blood were performed on samples obtained after overnight fasting. Analyses of fasting plasma triglycerides, total cholesterol, LDL, HDL, HbA1c, ASAT, ALAT, bilirubin, ALP, GT, PK, whole-blood glucose (fasting blood glucose), and insulin were carried out at the time of the baseline examination, and six and twelve weeks during the study. During the euglycaemic-hyperinsulinaemic clamp test, glucose concentration was determined every 5 minutes for 120 minutes, and insulin at 60 minutes and 120 minutes. All laboratory analyses were performed at the Department of Clinical Chemistry, Skåne University Hospital in Malmö, which is affiliated to a national standardization and quality control system. Insulin and glucose concentrations were measured using the same techniques as described above. Total cholesterol and HDL were measured with

enzyme assay kits, using an automated analyser (Aeroset™, Abbott Labs, USA). LDL was calculated using the Friedewald equation (107). All samples from each subject were analysed in the same run.

Insulin sensitivity

Insulin sensitivity was determined with the euglycaemic-hyperinsulinaemic clamp test, according to DeFronzo et al. (44). Intravenous catheters were inserted into the antecubital veins in both arms. One arm was used for the infusion of glucose and insulin, and the contralateral arm was used for intermittent blood sampling. The catheter was kept patent by a slow infusion of 0.9% saline, to which 2 mL of the subject's blood per 100 mL infusate had been added to prevent the absorption of insulin on glassware and plastic surfaces. Baseline samples of glucose and insulin were taken. A primed constant infusion of insulin (Actrapid 100 IU/mL; NovoNordisk, Bagsvaerd, Denmark), was started at a constant infusion rate of 0.28 nmol/m^2 body surface area/min. After 4 min, glucose infusion (200 mg/mL) was started; the infusion rate being adjusted manually throughout the procedure to maintain the blood glucose level at 5.0 mmol/L. Blood glucose concentrations was determined at the bedside every 5 minutes and were measured with the HemoCue Glucose system.

Statistical analyses

In Studies I, II and III the incremental area under the curve (AUC) was calculated for glucose, insulin and satiety (Paper II) for each subject and meal (using GraphPad Prism ver. 3.0; GraphPad Software, San Diego, CA, USA). All areas below the baseline were excluded from the calculations. The GI and the insulinaemic index (GII) were calculated by expressing each participant's glucose incremental AUC following the test meal as a percentage of their AUC following the reference meal. Descriptive statistics were run on all measures, and the results are given as means ± SEMs. All statistical calculations were performed using SPSS for Windows software (version 14.0, 2005). Differences in plasma glucose levels, insulin levels, GI, and the questions regarding satiety were evaluated with the Wilcoxon signed-rank test. Significance was set at $p \leq 0.05$.

The statistical calculations in Study IV were performed using SPSS for Windows software (version 22, 2013). The Wilcoxon signed-rank test was used to compare quantitative variables within the group, and the Mann-Whitney U test was used to compare quantitative variables between groups. Descriptive statistics were run on all measures, and the results are given as means ± SEMs. Pearson's chi-squared test for categorized variables was used to test for statistically significant differences between the groups. Values of $p < 0.05$ were considered to indicate statistically significant differences.

Results

The Effects of Turmeric

Postprandial plasma glucose response to turmeric

The results of Study I on the effects of turmeric on postprandial plasma glucose response are given in Figure 1 and Table 6. No statistically significant differences were found between plasma glucose responses at different times, or in the incremental areas under the postprandial glucose curves between 6 g turmeric or the reference using the Wilcoxon signed-rank test. No significant differences were seen in GI after ingesting 6 g turmeric or placebo, using the Wilcoxon signed-rank test, $p < 0.05$

Table 6. Postprandial plasma glucose area under the curve (AUC) and glycaemic index (GI) measured in 14 healthy subjects after the ingestion of 6 g turmeric or placebo capsules (reference). All values are means ± SEM, $p < 0.05$

	Glucose AUC (mU min/L)		**GI (%)**	
Time	**Turmeric**	**Reference**	**Turmeric**	**Reference**
0-90 min	229.6 ± 23.8	216.5 ± 27.4	137.9 ± 24.8	100
0-120 min	275.6 ± 28.3	253.9 ± 32.7	135.0 ± 20.7	100

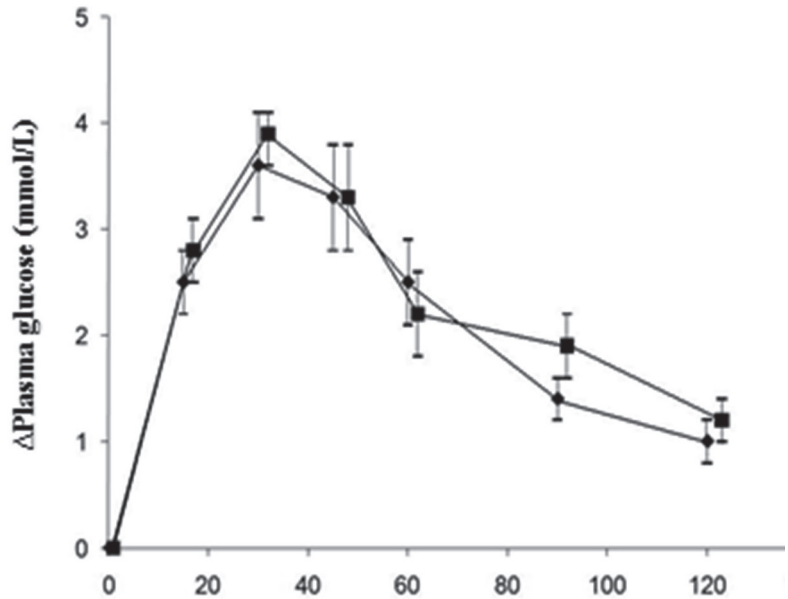


Figure 1. The mean (± SEM) incremental plasma glucose concentration in 14 healthy subjects measured with the OGTT after 6 g turmeric (■) or placebo capsules (♦).

The effects of turmeric on postprandial insulin response

Ingestion of 6 g turmeric resulted in a significantly higher serum insulin response at 30 min ($p = 0.048$) and 60 min ($p = 0.033$) compared to the reference. Insulin response in the postprandial phase (30-60 min) was also significantly higher than the reference (Figure 2). Significantly higher serum insulin AUCs were seen at 15 min ($p = 0.048$), 30 min ($p = 0.035$), 90 min ($p = 0.03$) and 120 min ($p = 0.02$) after the ingestion of turmeric than after the placebo capsules (Table 7). Significant differences in serum insulin AUCs were evaluated with the Wilcoxon signed-rank test, $p < 0.05$.

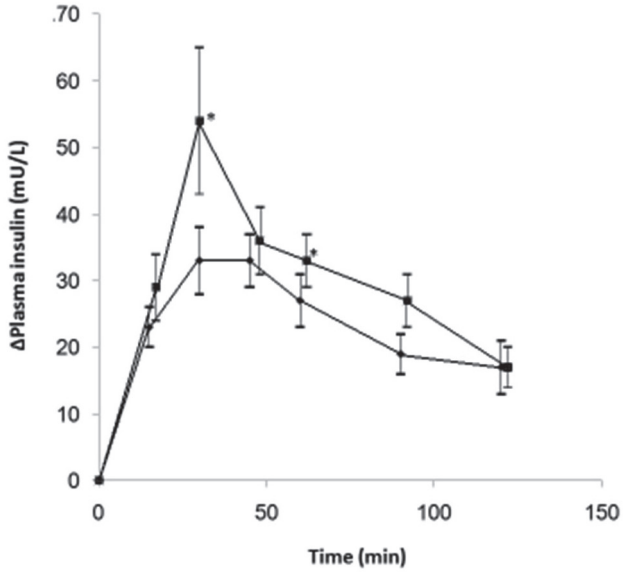


Figure 2. The mean (± SEM) incremental serum insulin concentration measured in 14 healthy subjects after ingesting 6g turmeric (■) or placebo capsules (♦). *Significant difference between the responses to turmeric or placebo, $p < 0.05$.

Table 7. Postprandial serum insulin area under the curve (AUC) in 14 healthy subjects after the ingestion of turmeric or placebo capsules (reference). All values are means ± SEM. * Significant differences between the responses with and without turmeric, $p < 0.05$.

	Insulin AUC (mU min/L)	
Time	Turmeric	Reference
0-15 min	217.5 ± 37.7*	169.2 ± 19.8
0-30 min	838.1 ± 152.7*	584.3 ± 61.2
0-45 min	1509.9 ± 252.2	1076.5 ± 111.4
0-60 min	2021.0 ± 285.9	1521.7 ± 147.3
0-90 min	2908.3 ± 353.0*	2210.3 ± 215.5
0-120 min	3570.9 ± 410.7	2749.5 ± 283.7

The effects of turmeric on GII

The ingestion of 6 g turmeric resulted in a significantly higher GII 90 min after the OGTT ($p = 0.024$), while no significant difference was seen in GII at 120 min (Table 8). Significant differences in GII were evaluated with the Wilcoxon signed-rank test.

Table 8. Postprandial insulinaemic index (GII) in 14 healthy subjects after the ingestion of turmeric or placebo capsules (reference). All values are means ± SEM. *Significant difference between the responses to the OGTT with and without turmeric, $p < 0.05$.

	GII (%)	
Time	Turmeric	Reference
0-90 min	136.4 ± 13.8*	100
0-120 min	130.0 ± 16.3	100

The Effects of Green Tea

Postprandial plasma glucose response to green tea

Ingestion of the green tea meal resulted in a significantly higher blood glucose response after 120 min than the reference meal ($p = 0.019$). The postprandial change in glucose level compared with the baseline value was also significantly higher after the green tea meal than the reference meal after 120 min (Figure 3). No significant differences were seen in the plasma glucose AUCs (Table 9).

Table 9. Postprandial plasma glucose AUC and serum insulin AUC in healthy subjects after the ingestion of a meal with or without green tea. All values are means ± SEM, n = 14 for glucose, n = 13 for insulin.

	Glucose		Insulin	
	AUC (mmol min/L)		AUC (mUmin/L)	
Time	Green tea	Reference	Green tea	Reference
0-15 min	7.1 ± 0.9	8.9 ± 1.7	124.3 ± 18.6	111.5 ± 15.6
0-30 min	39.1 ± 3.3	42.9 ± 5.4	542.8 ± 54.8	537.5 ± 60.5
0-45 min	88.4 ± 7.1	89.3 ± 9.3	1142.8 ± 88.2	1166.8 ± 109.2
0-60 min	127.9 ± 12.8	124.2 ± 13.3	1619.7 ± 103.9	1711.9 ± 131.6
0-90 min	179.5 ± 19.7	161.9 ± 21.4	2163.9 ± 148.2	2469.5 ± 175.2
0-120 min	204.3 ± 22.2	177.8 ± 24.7	2434.5 ± 168.5	2902.2 ± 224.0

Postprandial insulin response to green tea

No significant differences in serum insulin levels or insulin AUCs were observed between the green tea meal and the reference meal (Figure 3 and Table 9). Significant differences between the green tea or reference meals according to the Wilcoxon signed-rank test.

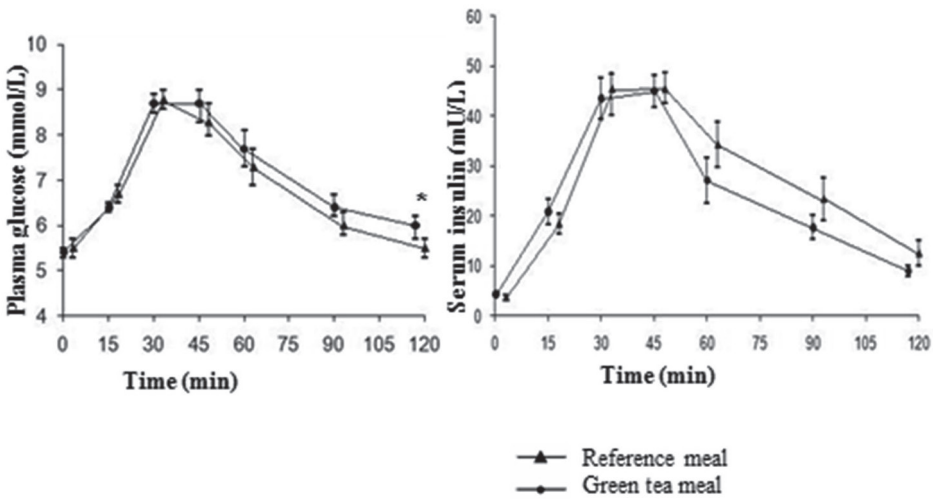


Figure 3. The mean (± SEM) incremental plasma glucose (n=14) and serum insulin (n=13) concentrations in healthy subjects after ingesting a green tea meal (●) and a reference meal (▲). *Significant difference between the responses to turmeric or reference, $p < 0.05$.

The effect of green tea on GI

No significant differences were seen in GI between the green tea meal and the reference meal.

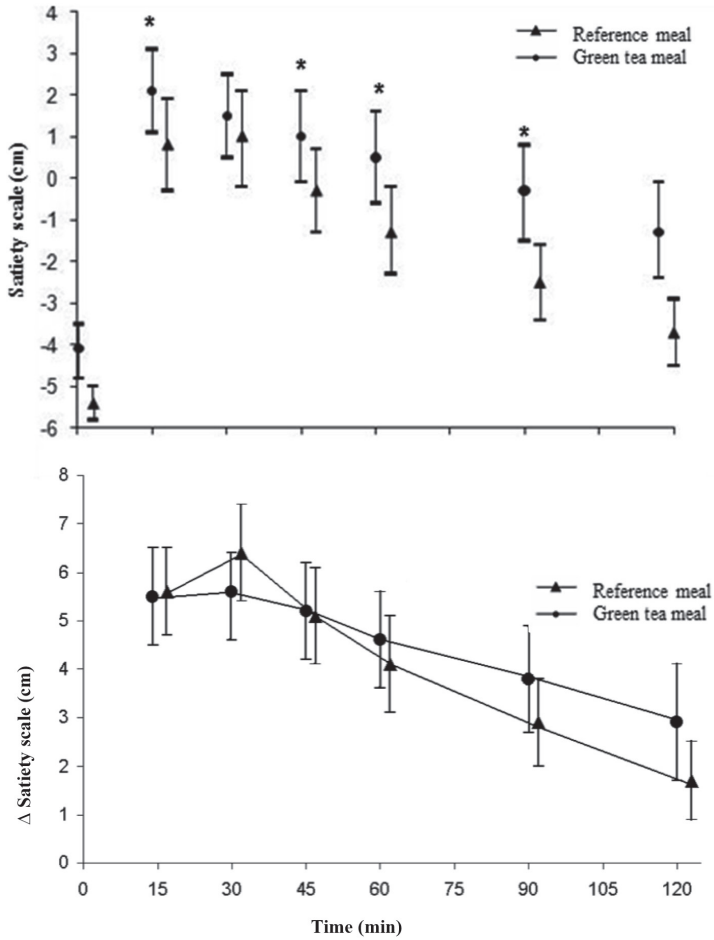


Figure 4. a) The mean (± SEM) satiety scores and b) incremental satiety scores in 14 healthy subjects after the ingestion of a green tea meal (●) and a reference meal (▲)*Significant difference between the meals, $p \leq 0.05$.

Table 10. Satiety and fullness AUCs in 14 healthy subjects after the ingestion of a meal with or without green tea. All values are means ± SEM.*Significant differences between the meals , $p \leq 0.05$.

	Satiety AUC (cm·min)		Fullness AUC (cm·min)	
Time	Green tea	Reference	Green tea	Reference
0-15 min	41.8 ± 7.6	42.3 ± 6.8	46.4 ± 9.1	34.6 ± 9.1
0-30 min	125.6 ± 21.6	1278 ± 22.7	140.4 ± 24.1	109.4 ± 26.2
0-45 min	206.7 ± 35.0	218.5 ± 35.5	235.7 ± 38.9	185.7 ± 40.6
0-60 min	280.6 ± 48.6	288.7 ± 48.6	298.8 ± 54.3	244.8 ± 56.5
0-90 min	412.0 ± 77.3	397.0 ± 73.0	478.6 ± 90.9*	342.7 ± 87.4
0-120 min	525.0 ± 105.5	478.5 ± 91.6	629.1 ± 126.3*	415.8 ± 109.4

The effect of green tea on various aspects of satiety

Ingestion of the green tea meal resulted in a significantly higher postprandial satiety at 15 min (p = 0.005), 45 min (p = 0.045), 60 min (p = 0.025) and 90 min (p = 0.030), than the reference meal (Figure 4a). However, the postprandial change in satiety score compared with baseline was not significantly different between the meals. (Figure 4b). The AUCs for satiety were not significantly larger after ingestion of the green tea meal than after ingestion of the reference meal at any time (Table 10). Significant differences between green tea or reference meals were avaluated with the Wilcoxon signed-rank test.

Regarding the questions on different aspects of satiety, subjects reported a higher degree of fullness after the green tea meal than after the reference meal at 15 min (p =0.054), 45 min (p = 0.050), 90 min (p = 0.032) and 120 min (p = 0.042). The subjects felt more strongly they had enough to eat after the green tea meal than after the reference meal at 45 min (p = 0.005), 90 min (p = 0.041) and 120 min (p = 0.034) (Figure 5).

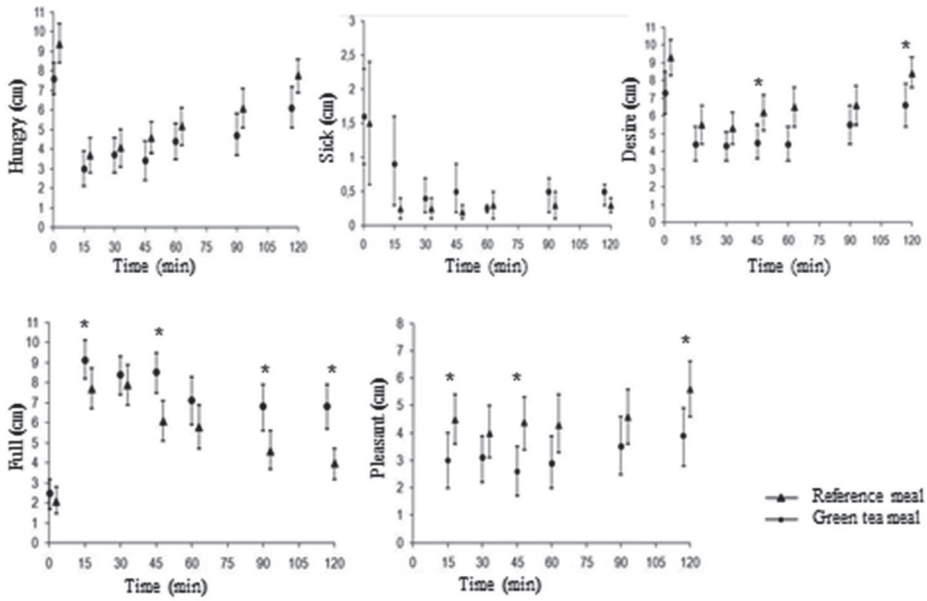


Figure 5. The mean (± SEM) scores for hunger, nausea desire, fullness, and pleasantness in 14 healthy subjects after the ingestion of a green tea meal (●) and a reference meal (▲).* Significant difference between the meals, p ≤ 0.05.

The change in postprandial fullness compared with baseline was also significantly higher after the green tea meal than after the reference meal at 120 min (p = 0.033). The AUCs for fullness were significantly greater at 90 (p = 0.016) and 120 min (p = 0.008) after ingestion of the green tea meal than after ingestion of the reference meal

(Table 10). No differences were observed in the intensity of hunger at any of the times studied (Figure 5). No differences were reported concerning how much the subjects liked or disliked the food; they rated the green tea meal and the reference meal as 4.6 ± 0.4 and 4.5 ± 0.4 (1-10), respectively. No differences were observed regarding the feeling of nausea (Figure 5). The desire to eat one's favourite food was significantly higher after the reference meal than after the green tea meal at 45 min ($p = 0.044$) and 120 min ($p = 0.025$) (Figure 5). After the reference meal, the subjects reported finding it more pleasant to eat another mouthful of the same food at 15 min ($p = 0.030$), 45 min ($p = 0.019$) and 120 min ($p = 0.015$) than after the green tea meal (Figure 5). Significant differences between the green tea or reference meals according to Wilcoxon signed-rank test.

The Effects of Ceylon cinnamon

Postprandial plasma glucose response to Ceylon cinnamon

No significant differences were seen in plasma glucose responses at different times, or in the incremental areas under the postprandial glucose curves between 6 g Ceylon cinnamon or reference, when evaluated with the Wilcoxon signed-rank test. (Figure 6 and Table 11)

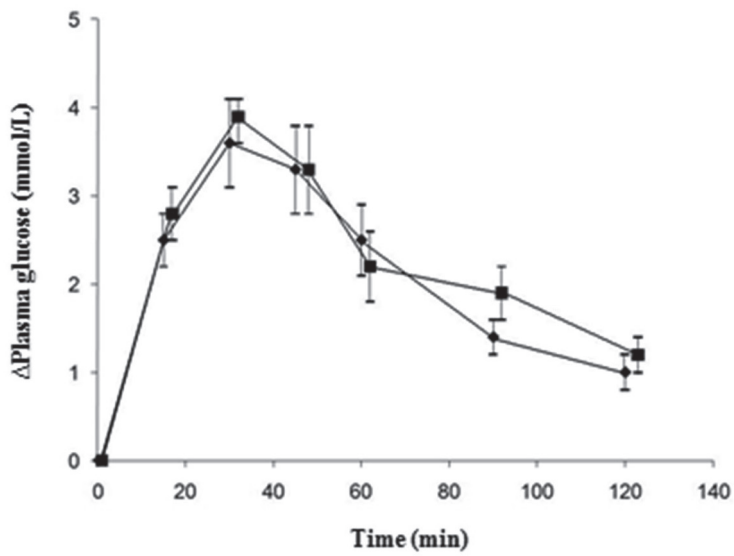


Figure 6. The mean (± SEM) plasma glucose concentration in ten subjects with impaired glucose tolerance following after ingesting Ceylon cinnamon (♦) or placebo capsules (■).

Postprandial insulin response to Ceylon cinnamon

No significant differences were seen in insulin responses at different times or in the incremental areas under the postprandial insulin curves, between 6 g Ceylon cinnamon or reference, when evaluated with the Wilcoxon signed rank sum test (Figure 7 and Table 11).

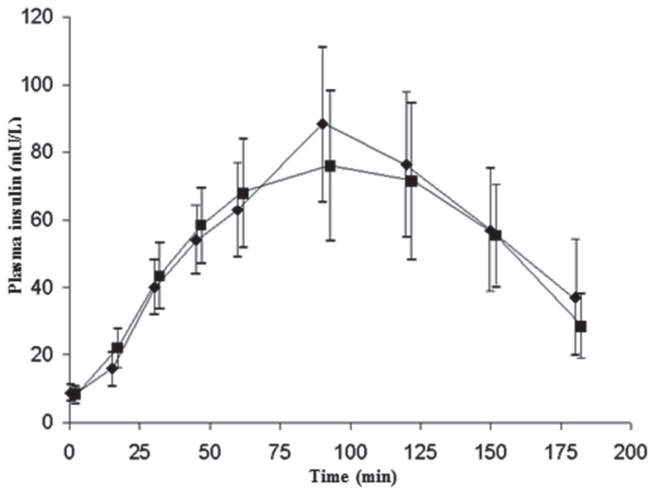


Figure 7. The mean (± SEM) plasma insulin concentration in ten subjects with impaired glucose tolerance after ingesting Ceylon cinnamon (♦) or placebo capsules (■).

The effects of Ceylon cinnamon on GI and GII

No significant differences were seen in GI or GII between the OGTT with and without 6 g Ceylon cinnamon when evaluated with the Wilcoxon signed-rank test (Table 11).

Table 11: The mean (± SEM) postprandial plasma glucose area under the curve (AUC), plasma insulin AUC, the glycaemic index (GI) and insulinaemic index (GII) in subjects with impaired glucose tolerance after ingesting Ceylon cinnamon or placebo capsules (reference).

	Ceylon cinnamon	Reference
	Mean ± SEM	Mean ± SEM
GI (%)	98 ± 10	100
Glucose AUC (mmol/L per min)		
0-150 min	615.6 ± 56.2	668.0 ± 84.5
0-180 min	659.2 ± 64.5	709.5 ± 85.3
GII (%)	109 ± 15	100
Insulin AUC (mU/L per min)		
0–150 min	7668.0 ± 1785.2	7512.7 ± 1987.5
0–180 min	8834.4 ± 2167.8	8523.6 ± 2236.5

The Effects of Cassia cinnamon

Anthropometric measurements

No significant changes were seen in clinical or demographic characteristics such as BMI, waist:hip ratio, systolic or diastolic blood pressure between the group ingesting 12 g cassia cinnamon/day for 12 weeks and the reference group.

Effects on glycaemic outcomes, lipids and liver enzymes

Table 12 gives information regarding Cassia cinnamons effect on glycaemic outcomes, lipids and liver enzymes. Significant differences on glycaemic outcomes, lipids and liver enzymes between the treated group and the reference group were evaluated at baseline with the Mann-Whitney U test (p-value[1]). Significant differences in glycaemic outcomes, lipids and liver enzymes within the groups were evaluated at 12 weeks with the Wilcoxon signed rank test (p-value[2] for Cassia cinnamon and p-value[3] for reference).

No significant differences were found in HbA1c or fasting blood glucose between the group given Cassia cinnamon and the reference group. No significant differences were found in insulin levels between the groups at baseline, but the reference group had a significantly lower fasting insulin level than the treated group after 12

weeks. No significant differences were seen in total cholesterol, LDL cholesterol, HDL cholesterol, or triglycerides at baseline between the treated group and the reference group, and there were no significant changes during the study. No significant differences were seen in ALAT, ALP, GT or bilirubin at baseline, and there were no significant changes during the study between the treated group and the reference group.

Table 12. Glycaemic outcomes, and effects on lipids and liver enzymes in patients with IGT, at baseline and after 12 weeks' treatment with Cassia cinnamon or the reference Values given are means ± SD, * $p < 0.05$.

Variable	Baseline			After 12 weeks			
	Cassia cinnamon	Reference	p-value[1]	Cassia cinnamon	p-value[2]	Reference	p-value[3]
Fasting glucose (mmol/L)	6.0 ± 0.3	6.7 ± 0.4	0.370	6.1 ± 0.4	0.735	6.1 ± 0.4	0.205
Fasting insulin (Um/L)	9.8 ± 2.1	11.1 ± 2.0	0.481	9.0 ± 2.5	0.284	8.5 ± 1.6	0.034*
HbA1c (mmol/mol)	39.6 ± 1.3	40.1 ± 2.4	0.815	40.2 ± 1.6	0.320	40.1 ± 1.8	0.786
Cholesterol (mmol/L)	4.9 ± 0.4	4.5 ± 0.2	0.673	4.6 ± 0.3	0.482	4.4 ± 0.2	0.670
LDL cholesterol (mmol/L)	3.2 ± 0.4	2.7 ± 0.2	0.606	2.9 ± 0.2	0.553	2.6 ± 0.3	0.528
HDL cholesterol (mmol/L)	1.4 ± 0.1	1.5 ± 0.1	0.888	1.4 ± 0.1	0.414	1.5 ± 0.1	0.774
Triglycerides (mmol/L)	1.1 ± 0.1	1.1 ± 0.1	0.888	1.0 ± 0.1	0.101	1.0 ± 0.2	0.686
ASAT (µkat/L)	0.40 ± 0.05	0.38 ± 0.04	0.888	0.41 ± 0.05	0.445	0.38 ± 0.04	0.752
ALAT (µkat/L)	0.50 ± 0.09	0.39 ± 0.07	0.481	0.49 ± 0.09	0.799	0.38 ± 0.08	0.528
ALP (µkat/L)	1.04 ± 0.13	0.89 ± 0.05	0.541	1.10 ± 1.28	0.128	0.86 ± 0.06	0.161
GT (µkat/L)	0.58 ± 0.15	0.37 ± 0.07	0.370	0.71 ± 0.25	0.313	0.36 ± 0.06	0.674
Bilirubin (µmol/L)	9.9 ± 1.6	9.2 ± 1.1	0.963	11.6 ± 2.0	0.087	8.5 ± 1.1	0.197
Pk- INR	1.0 ± 0.02	1.04 ± 0.02	0.888	1.0 ± 0.02	0.317	1.01 ± 0.02	0.157

Effect of Cassia cinnamon on insulin sensitivity

No significant increase in insulin sensitivity was seen in the treated group after 60 or 120 min (Table 13). A significant increase in insulin sensitivity was seen in the reference group at 60 min, but not at 120 min. Significant differences in insulin sensitivity within the groups were evaluated at 60 min and 120 min at baseline and after 12 weeks with the Wilcoxon signed-rank test.

Table 13. Insulin sensitivity measured by euglycaemic-hyperinsulinaemic clamp in patients with IGT, at baseline and after 12 weeks' treatment with Cassia cinnamon or placebo capsules (reference). Values are means ± SD, *p<0.05.

	Baseline	12 weeks	p-value	Baseline	12 weeks	p-value
	Cassia cinnamon (n=9)			Reference (n=8)		
60 min	7.3 ±1.3	7.8 ± 1.4	0.477	6.3 ± 1.2	8.8 ±1.9	0.012*
120 min	6.0 ± 1.1	6.3 ± 0.9	0.373	5.3 ± 1.8	7.0 ± 1.2	0.068

Discussion

The aim of the studies described in this thesis was to identify functional foods that could reduce blood glucose and insulin, and increase satiety to help prevent the escalating prevalence of diabetes and overweight.

Results Obtained with Turmeric

Ingestion of 6 g turmeric followed by an OGTT increased the postprandial serum insulin concentration without affecting the plasma glucose in healthy subjects (Paper I). This could indicate that turmeric has an effect on insulin secretion, which is consistent with the results of an *in vitro* study showing that curcumin enhances insulin release in pancreatic beta-cells (108). However, no significant increase in insulin was seen after 120 min, and there was no change in postprandial glucose. The results of previous *in vitro* studies have indicated that turmeric can have several affects, all of which increase insulin sensitivity (108). Insulin sensitivity is not a problem in healthy subjects and a higher level of insulin may only start the feedback loop including gluconeogenesis, instead of having effects on postprandial plasma glucose. The body has different means of avoiding hypoglycaemia, and glucose levels are strictly regulated in healthy subjects. This could explain why no significant differences were seen in plasma glucose levels or insulin after 120 min in this study (Paper I), however this requires further research.

The active component in turmeric is curcumin, and it is believed to be the agent responsible for most of the biological activity of turmeric, including its antidiabetic properties (79). It has been estimated that turmeric contains about 2-8% curcumin (79), and a review of a number of trials studying the efficacy of curcumin revealed poor absorption and low bioavailability. Only 0.4-3.6 μM curcumin was found in human serum after an intake of 4-8 g curcumin. The explanations given for the low levels of curcumin in plasma and tissue include poor absorption, insolubility in water, high rate of metabolism and rapid systemic elimination (109). Methods of increasing the absorption and systemic bioavailability of curcumin have been studied with varying results (110). It is impossible to consume 6 g turmeric on its own because of its taste, and its poor bioavailability and thus low absorption make

it difficult to include turmeric in functional foods. The aim of the work described in this thesis was to gain knowledge on possible nutritional interventions in an attempt to find functional foods that could prevent diabetes and, thus, indirectly cardiovascular disease. When the active component of turmeric has to be extracted and then combined with an absorption factor to increase its bioavailability, it can no longer be classed as a functional food.

Results Obtained with Green Tea

The ingestion of 300 mL green tea did not lower plasma glucose, GI or insulin levels in healthy subjects; however, they reported significantly higher satiety and fullness after the consumption of tea than after water.

The most abundant and active component in green tea is EGCG, and an *in vitro* study of EGCG has shown it to have antidiabetic effects, by increasing insulin activity (111). Green tea has also been found to increase the basal and insulin-stimulated glucose uptake of rat adipocytes (112), suppress glucose absorption in the rabbit small intestine (113), and ameliorate insulin resistance by increased expression of glucose transporter IV in rat adipocytes (114). In addition, EGCG has been found to exhibit antidiabetic properties by suppressing gluconeogenesis in rat hepatic cells (115). Findings from cross-sectional and cohort animal studies have indicated that green tea has an effect on glucose tolerance but intervention studies gave conflicting results (95-100).

No decrease in glucose levels was found after ingesting green tea meal and, contrary to what was expected, the 120 min glucose value was higher following the green tea meal than the reference meal. Park et al. made a similar observation, and suggested that the catechins had a *hypoglycaemic* effect in the intestines, but a *hyperglycaemic* effect later in the circulation. This conclusion was drawn after observing significantly lower glucose levels during the first hour of an OGTT after the ingestion of green tea, followed by a significantly higher level after 2 hours. They compared these observations with another test in the same study in which the patients ingested green tea an hour before the OGTT. Two hours after the ingestion of the green tea (one hour after the OGTT) the glucose level was significantly higher in the treated group, but 3 hours after green tea ingestion (2 hours after the OGTT) the glucose levels were the same in the treated and the control group (116). Tsuneki et al. reported an immediate glucose-lowering effect of green tea powder after an OGTT in healthy humans (117). We studied the immediate effects of green tea on glucose metabolism after the ingestion of a white bread meal, our findings concluded that green tea does not lower glucose or insulin levels. Previous results on the effects of green tea have been ambiguous, and the discrepancy between results from human and animal studies may reflect species-specific differences. Possible reasons

for the inconsistent results *in vivo* might be individual variations in the bioavailability and metabolism of catechins in humans (90).

Flint et al. concluded that the scoring of sensations such as hunger, satiety, fullness and desire using a VAS was reproducible, and could therefore be used in single-meal studies (118). In the present work, the VAS scores revealed an overall higher sensation of satiety after the green tea meal than after the reference meal (Paper II). This is supported by the fact that not only was satiety increased, but also the feeling of fullness and the feeling of having had enough to eat. These findings are consistent with those of Nagao et al., who found a decrease in waist circumference in T2DM patients after 12 weeks of treatment with 582.8 mg of catechins (100). Auvichayapat et al. found a significant reduction in BMI during a 12-week intervention in obese subjects on a standardized diet with green tea capsules, but no effect was seen on satiety (119).

Several factors may have contributed to the positive findings in the present study, for example, the crossover design, the recording of different sensations of satiety at frequent intervals, and serving the green tea in its natural form as a hot beverage. The taste perception of the green tea may have been responsible for the satiety-promoting effect, contributing to a stronger sensation of satiety after the green tea meal than after the reference meal. Oral exposure to food is related to an increase in satiety, and a decrease in hunger and desire to eat (120). Measurements of taste perception of the meals would have provided additional information. However, the participants did not dislike the green tea meal more than the reference meal, nor did they feel any more nauseous during the green tea meal, so the higher level of satiety could not be explained by any unpleasantness produced by the green tea meal. The subjects experienced a stronger desire to consume their favourite food or eat another mouthful of the same food after the reference meal. Since the same kind and amount of food was ingested on both occasions, greater distension of the stomach is not likely to be the mechanism behind these findings.

The postprandial glucose concentration is determined by the rates of glucose formation and clearance. Insulin mediates glucose uptake in the tissues after a meal. The gastric emptying rate, together with other factors, regulates the postprandial glucose response, and a reduction in the gastric emptying rate leads to a lower postprandial glucose concentration. Since green tea did not lower postprandial glucose or insulin levels, we can assume that a reduction in the gastric emptying rate is not a likely explanation of the increased satiety or fullness. Postprandial changes in hormones may be responsible for the satiety-promoting effect of green tea (121-123). However, such changes in hormones were not studied in this work. The satiety signalling process is very complex, and involves several gastrointestinal peptides and neurotransmitters (122). Norepinephrine plays an important role in satiety signalling in the hypothalamus (123). Green tea catechins have been shown to inhibit catechol-o-methyl-transferase, an enzyme that degrades norepinephrine in the synaptic cleft (121). This would lead to prolonged action of norepinephrine, and is

one possible explanation of the effect of increased satiety seen after drinking green tea. However, it is uncertain whether polyphenols can cross the blood-brain barrier (124).

A limitation of this study was that the study was not blinded, and the possibility that the findings of greater satiety with green tea could be biased cannot be excluded. Furthermore, the effect of green tea on satiety was only a secondary endpoint, and the subjects included were healthy and of normal weight. The results may have been different with overweight and obese subjects. To simplify the comparison of the glucose AUC calculations the results are presented in terms of GI. No difference in GI was found as a result of green tea, possibly due to large inter- and intrasubject variations in AUCs. The precision could have been improved if the test and reference meals had been repeated.

The results of this study suggest that green tea may increase satiety and fullness. Clearly, a larger clinical trial involving a greater number of overweight and obese subjects is needed to further evaluate the effects of green tea on satiety.

Results Obtained with Cinnamon

Ingestion of 6 g Ceylon cinnamon followed by an OGTT had no effect on postprandial plasma glucose or serum insulin in patients with IGT (Paper III). Neither was any improvement seen in fasting plasma glucose, insulin, blood lipids or insulin sensitivity in patients with IGT after 12 weeks of Cassia cinnamon supplementation (12 g/d). No significant changes were seen in liver enzymes (Paper IV).

A meta-analysis performed in 2008 revealed no effect of ingested cinnamon on glucose or lipid parameters in subjects with T2DM (125). In contrast, a new meta-analysis in 2013 of T2DM patients revealed a decrease in fasting plasma glucose, HbA1c, total cholesterol, LDL and triacylglycerol levels, and an increase in HDL, but no change in HbA1c, after the ingestion of cinnamon (126).

Cinnamon has demonstrated qualities that enhance glucose uptake by activating insulin receptor kinase activity, autophosphorylation of the insulin receptor, and glycogen synthase activity, *in vitro* and *in vivo* (61, 62, 64, 127-130). Human studies have provided interesting results regarding the antidiabetic properties of cinnamon, and differences have been found between Western and Asian populations.

Diabetes is a complex disease and research is ongoing into the genetics of the disease. But it is a major challenge to find the genes that affect the disease sensitivity when the disease is multifactorial. Over the past 10 years more than 40 types of T2DM-associated genes have been identified, but these still explain less than 10% of T2DM heritability (14). Significant genetic differences have been found between Asians and Europeans (131). One of the most frequently discussed differences is in mitochondrial DNA (mDNA), which has a higher frequency in Asians than in

Europeans. mDNA and adenosine triphosphate (ATP) are closely linked, and as ATP plays a critical role in the production and release of insulin, mDNA could be associated with T2DM (132). Park et al. also found that mDNA (16189) significantly increased the risk of developing diabetes in Asians but was negatively associated with T2DM in Europeans (126). It has been found that the creatine phosphate shuttle and mitochondrial phosphorylation rates were decreased by 20% and 30%, respectively, in 14 insulin-resistant offspring of diabetic parents (133). This may indicate an inherited defect in mitochondrial oxidative phosphorylation rates (133).

It has been demonstrated in *in vitro* and *in vivo* studies that cinnamon is involved in insulin receptor activity and glycogen synthase, but cinnamon may play a different roll in Western populations than in Asians. Khan et al. and Askari et al. found that cinnamon had antidiabetic properties in subjects from Pakistan and Iran, respectively (52, 68), in contrast to Vanschoonbeek et al. and Blevins et al. who found no evidence of any antidiabetic properties of cinnamon in populations in the Netherlands and USA, respectively (71, 72). In the present study, no antidiabetic effect of cinnamon was found on a Swedish population. These differences in findings could be due to genetic differences, however, polygenetic predisposition and the complexity of the disease makes it difficult to determine which factors are responsible. The interaction between genetic variations and environmental factors may thus be of greater importance than previously thought.

The effects of the origin, type and form of cinnamon have also been discussed. Broadhurst et al. reported that both cassia and Ceylon cinnamon had stronger insulin-enhancing biological activity than other spices (61). *Cinnamomum burmannii* has also been found to have antidiabetic properties (62). In the present studies commercially prepared Ceylon and Cassia cinnamon were used in the powder form. The insulin-enhancing biological activity of several kinds of commercially prepared cinnamon from Indonesia, China and Vietnam has been studied *in vitro*, showing that the activities of the different species and samples were similar (62). These results suggest that the type of cinnamon administered is less important, and that the conflicting results may be due to differences in the dose of cinnamon administered, the duration of the study, and/or the population studied.

In a recent study, HbA1c was found to be decreased in patients with T2DM receiving 1 g *C. cassia* per day for 12 weeks (134). Similar results were reported by Akilen using a dose of 2 g *C. cassia* per day for 12 weeks, and by Lu at doses of 120 mg or 360 mg *C. aromaticum* per day for 12 weeks (135, 136). In these studies, the subjects had HbA1c levels above 8% and high fasting glucose levels, and were already taking medication for Hyperglycaemia. The subjects in the studies described in Papers III and IV had IGT, normal HbA1c levels, and were not taking any medication for diabetes. These results suggest that individuals with poorly controlled diabetes may benefit more from cinnamon intake than those receiving adequate treatment.

The strengths of Studies III and IV were: the design; a crossover blinded trial with no drops-out (Paper III) and a randomized, double-blind placebo-controlled design with few drop-outs (Paper IV), and the direct measurement of insulin sensitivity. However, the studies also had some limitations. Firstly, the sample sizes were small in both studies, and all the participants were living in southern Sweden. Secondly, although the cinnamon and placebo capsules appeared identical, it is possible that some of the participants could discern a difference between the two types of capsules because of the smell. Thirdly, the control group in Study IV had a significantly lower insulin response than the treated group after 12 weeks, which indicates that the placebo capsules had an active effect. The placebo capsules contained cellulose, which is a type of fibre, and the amount of fibre was probably sufficient to cause an effect on the gastrointestinal tract, leading to an indirect effect on insulin response. The relation between high-fibre diets and a low insulin response is already known (4). Finally, the compliance was not determined precisely in Study IV, but was assessed by counting the remaining capsules and repeated follow-ups.

General Limitations

We did not monitor the subjects' choice of food or amount of exercise the night before the tests, which may have affected the postprandial blood glucose responses, especially in Studies I-III. Another limitation of the present work is that the sample sizes were small, and only the immediate effects on glucose and insulin levels were determined in Studies I-III. Clearly, larger trials involving a greater number of subjects are needed to validate the findings of these studies.

Summary in Swedish

Populärvetenskaplig Sammanfattning

I dagens välfärdsländer är typ 2 diabetes, övervikt och hjärt-kärlsjukdomar ett växande problem. Dessa följdsjukdomar av ett ohälsosamt leverne är mycket kostsamma, dels för samhället men även för individen. En enkel kostbehandling som minskar nivån av cirkulerande blodsocker skulle kunna minska risken för utveckling av dessa välfärdssjukdomar.

Orsaken till typ 2-diabetes är nedsatt insulinkänslighet. Insulin tillverkas i kroppen, i bukspottkörteln, för att därifrån spridas ut i hela kroppen med blodet. Nedsatt insulinkänslighet innebär att insulinet inte längre fungerar lika effektivt i muskler, lever och fettvävnad. Sockret i blodet behövs för att muskler, lever och fettvävnad ska kunna fungera. För att sockret ska kunna komma in i cellerna behövs insulin. Nedsatt insulinkänslighet medför att sockermolekyler stannar kvar i blodbanan. Till slut leder detta till att sockret reagerar med röda blodkroppar och blodfetter, som i sin tur fastnar i kärlväggen. Detta tror man utlöser en inflammation i kärlväggen, vilket så småningom resulterar i åderförkalkning.

IGT (Impaired glucose tolerance) är ett tillstånd där individen har lätt förhöjda blodsockernivåer i fasta och efter en sockerbelastning. IGT anses vara en stor riskfaktor för utveckling av diabetes och räknas därför som ett förstadium till diabetes.

Huvudsyftet med denna avhandling var att försöka finna kost som är hälsofrämjande, framförallt avseende diabetes, i både förebyggande syfte men även för att minska komplikationer till följd av diabetes.

Gurkmeja

Gurkmeja har tidigare, framförallt i studier med möss, uppvisat egenskaper som främjat insulinkänslighet. Det aktiva ämnet i gurkmeja heter curcumin och i djurförsök har man sett att curcumin påverkar, via en rad olika mekanismer, insulinkänslighet och blodfetter. Inga kliniska studier var tidigare gjorda på människor och vi ville undersöka om gurkmeja sänker blodsocker- och insulinnivåer.

Studie I

Fjorton friska individer serverades en glukosbelastning med kapslar med gurkmeja ena gången och utan gurkmeja nästa gång. Blodsocker och insulin mättes varje 15:e minut upptill 150 minuter efter intag. Ingen statistiskt säkerställd skillnad i blodsockernivå uppmättes men gurkmeja gav ett betydande högre insulinsvar.

I cellstudier har man funnit att curcumin i gurkmeja påverkar bukspottskörtelns celler till att utsöndra insulin. I vår studie fick vi ett högre insulinsvar men ingen skillnad i blodsocker, vilket kan anses märkligt. Men i friska individer är sockernivån i blodet mycket välreglerat och korrigeras snabbt vid tendens till lågt blodsockervärde. Förmodligen var detta en del av förklaringen. Det behövs fler humana studier då vår studie var en liten studie med en mätmetod som endast utskilde den direkta effekten på insulin och blodsockersvar. Problemet med gurkmeja och curcumin, är att kroppens upptagningsförmåga är extremt låg och därför behövs stora mängder för att uppnå hälsofrämjande effekter. Stora mängder av gurkmeja är omöjligt att inta, på grund av sin smak och konsistens, och gurkmeja förlorar därmed sin plats som kostbehandling.

Grönt te

Många studier har genomförts med fokus på grönt te och dess antioxidanta egenskaper. Avseende grönt te och dess effekt på insulinkänslighet har resultaten varit motstridiga. Grönt te innehåller antioxidanter som kallas för katechiner. För att öka insulinkänslighet är den mest aktiva katechinen den s.k. epigallokatechin gallate. Vi

ville undersöka om grönt te kan påverka insulinkänsligheten men även mättnadsgraden.

Studie II

Fjorton friska försökspersonerna serverades en måltid bestående av 50 g kolhydrater med ena gången grönt te och andra gången varmt vatten. Blodsocker och insulin mättes varje 15:e minut upptill 120 minuter efter intag. Ingen statistiskt säkerställd skillnad i insulinnivå uppmättes men en betydande skillnad i blodsockersvar samt mättnadsgrad uppmättes där grönt te gav ett högre blodsockersvar samt en längre mättnadskänsla.

Resultatet blev delvis i motsats till vad vi hade förväntat oss. Blodsockersvaret var högre vid intag av grönt te jämfört med referensen men individerna kände en högre mättnadsgrad. Det finns studier som försökt hitta orsaken till det förhöjda blodsockersvaret genom att testa att ge grönt te vid olika tidpunkter. Grönt te har då primärt haft en sänkande effekt på blodsockret men efter tid har blodsockersvaret stigit. Spekulationer kring grönt te och dess effekt på olika vävnader har påbörjats men ännu är detta oklart.

Aptit och mättnad är komplext och involverar många organ i kroppen. I vår studie fick vi signifikant högre mättnadsgrad, där förklaringen förmodligen är multifaktoriell. Grönt te och dess aktiva substans har i cellstudier påverkat hjärnan och aptitcentrat men humana studier har gett olika resultat. Vår studie var liten samt mätte endast den direkta effekten, således behövs det dels långtidsstudier men även ett högre deltagarantal.

Kanel

I tidigare cell- och djurstudier har antioxidanter från kanel visat sig öka blodsockerupptaget genom att höja insulinkänsligheten. Om kanel skulle kunna hjälpa till att höja insulinkänsligheten, så betyder det alltså att kanel indirekt skulle kunna minska uppkomsten av åderförkalkning.

Intresset för kanel och dess effekt hos patienter med typ 2 diabetes blev stort efter en studie i Pakistan, där patienterna fick en betydande sänkning av både blodsocker och blodfetter efter ett intag av kanel. I västvärlden har studier med motstridiga resultat redovisats, vilket har resulterat i olika hypoteser. En hypotes anses vara att patienter med typ 2 diabetes i västvärlden är mycket väl behandlade och har inte samma nytta av ett intag av kanel. En annan hypotes att det är stor variation avseende kanelsorter, dosering samt behandlingslängd.

Vår forskargrupp har i tidigare studier på människor visat att ett intag av 6 g (engångsdos) av ”vanlig” kanel (sorten Cassia) sänker blodsockersvaret signifikant jämfört med placebo. I studien fick försökspersonerna äta risgrynsgröt utan kanel ena

gången och med kanel andra gången. Neutral risgrynsgröt har ett GI (glykemiskt index) på 100, men med 6 g kanel sänktes detta till 56.

Cassiakanelen innehåller ett ämne som heter koumarin, som enligt vissa anses vara skadligt för levern vid för höga doser. Därför beslutade vi oss för att genomföra en studie med en annan kanelsort, Ceylonkanel, som innehåller lägre halter koumarin. I cellförsök har båda sorterna av kanel visat upp positiva effekter på insulinkänsligheten.

Studie III

Tio individer med IGT serverades en glukosbelastning med kapslar med Ceylonkanel ena gången och utan Ceylonkanel nästa gång. Blodsocker och insulin mättes varje 15:e minut upptill 180 minuter efter intag. Ingen statistiskt säkerställd skillnad i blodsocker- eller insulinnivå uppmättes.

Ceylonkanel innehåller låga doser av koumarin och vissa studier tyder på att det är just koumarin som har positiva egenskapen att motverka diabetes, vilket kan förklara vårt resultat. Koumarins toxiska effekt på levern har varit omdiskuterat och ifrågasatt.

Studier avseende Cassiakanel har även fått motstridiga resultat och dess effekt på insulinkänslighet har tidigare bekräftats med indirekta mätmetoder. En direkt mätmetod av insulinresistens är euglykemisk hyperinsulinemisk clamp (förklaras nedan). Vi ville verifiera hypotesen (med hjälp av clamping) att Cassiakanel ökar insulinkänsligheten hos patienter med nedsatt insulinkänslighet samt att den inte påverkar levern.

Vid euglykemisk hyperinsulinemisk clamp är patienten fastande och en nål sätts i vardera armen. I den ena armen kopplas ett insulindropp, och mängden insulin beräknas utifrån patientens kroppsyta. I den andra armen kopplas ett 20 % sockerdropp. Under de första 10 minuter justeras insulinet enligt en speciell beräkning s.k. ”insulintrappa” och följs därefter av en underhållsdos i 120 minuter beräknat på 80 mU/m^2 kroppsyta/min.

Målet är att hålla blodsockernivån konstant, på en normal fastenivå på ca 5,0 mmol/L. För att uppnå detta tas blodsockermätningar var 5:e minut och hastigheten av tillsats socker justeras genom att öka eller minska sockerdroppet. Dropphastigheten av socker de sista 60 minuterna av undersökningen fungerar som ett mått på individens insulinkänslighet.

En individ som har en normal insulinkänslighet kräver större mängder socker för att hålla sockernivån normal. Däremot kräver en individ som har en nedsatt insulinkänslighet nästan inget socker, vilket tyder på insulinresistens.

Studie IV

I studie IV ingick 21 individer med IGT, med 10 respektive 11 personer i varje grupp. Matchade i ålder, kön och BMI, jämfördes grupperna efter ett intag

av kapslar motsvarande 6 g Cassiakanel två gånger om dagen med placebokapslar. Försökspersonerna följdes under 12 veckor. Förändring av BMI, blodfetter, leverprover, blodsockersvar mättes fastande v 0, v 6 och v 12. Förändringar i insulinresistens mättes med hjälp av euglykemisk hyperinsulinemisk clamp (se ovan). Inga statistiskt säkerställda skillnader i insulinkänslighet eller leverprover uppmättes.

Trots höga doser cassiakanel såg vi ingen förändring avseende insulinkänsligheten, men dock inte heller någon förändring i leverprover. Det finns vissa studier som har påvisat positiva resultat mot diabetes vid behandling med Cassiakanel och andra som inte har kunnat påvisa detta. Vad denna skillnad beror på är oklart men i nuläget finns det inget bevis, utifrån våra studier, att behandla med varken Cassia- eller Ceylonkanel för att motverka diabetes.

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