The role of formula diets with different macronutrient composition in the treatment of obesity

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Abstract

Background and aim: Today, overweight and obesity have become a major public health problem. While formula diets as meal replacements are evident for weight loss, the optimal macronutrient composition to facilitate weight loss and improving potential adverse effects is still in the focus of interest. In the context of current discussion of „low carb“ vs. „low fat“ diets, there is much debate about different macronutrient relations of formula diets used as meal replacements. Next to the relation of macronutrients, diets with a low glycemic index may induce higher satiety, which reduces energy intake and results in weight loss. Thus, this thesis investigates the efficacy of two isoenergetic formula diets with different focus on carbohydrates, proteins and fats.

Methods: 160 overweight and obese (BMI 27.9–35.1 kg/m^2) men and women were included in a randomized clinical trial and divided into two groups (high carbohydrate formula diet and high protein formula diet (HP)) of 80 matched subjects. They underwent an intervention for eight weeks, which consisted of three phases: (1) week 1 and 2: total replacement of three meals, (2) week 3 and 4: replacement of two meals and (3) week 5 to 8: replacement of one meal. Moreover, a cross-over trial with 20 healthy volunteers was conducted to determine the glycemic index and satiety of both formula diets.

Results: Within the weight reduction trial both formula diet groups showed a significant reduction of anthropometric data, body composition, metabolic parameters of the carbohydrate and fat metabolism and classic inflammation markers. Additionally, the formula based low calorie diet reduced inflammatory arachidonic acid derived oxylipins. Furthermore, the result indicates that the high protein formula diet can be classified as low GI food and the high carbohydrate formula diet as a medium GI food.

Conclusion: The data demonstrates that even in a short period of time both formula diet strategies had a similar influence on weight loss and are effective in improving body composition and reducing metabolic risk parameters. Moreover, no relation of glycemic index and satiety on energy intake has been observed. Therefore, the relation of macronutrients in formula diets is not crucial for effective formula diets. The focus should be on finding an individualized dietary approach. In future, further investigations have to clarify the physiologic systems that govern food intake and energy balance to fully realize the advantages of macronutrient composition in weight loss.

Trial registration: German Clinical DRKS00005481

Keywords: Carbohydrate, Protein, Formula diet, Obesity, Weight loss, Metabolic risk parameters, Glycemic index

Zusammenfassung

Hintergrund und Ziele der Arbeit: Übergewicht bzw. Adipositas stellt in Deutschland und anderen Industrienationen das zentrale und stetig wachsende Gesundheitsproblem dar. Eine wesentliche Maßnahme der Adipositastherapie ist die Energierestriktion. Hierbei besitzen sogenannte Formuladiäten, welche als Mahlzeitenersatzstrategie eingesetzt werden, einen bedeutenden Stellenwert. Im Zuge der vielfach zu findenden „low carb-“ vs. „low fat“-Debatte wird zudem inzwischen vermehrt diskutiert, ob unterschiedliche Relationen der Makronährstoffe in Formuladiäten einen Einfluss auf die Gewichtsreduktion sowie Parameter des Kohlenhydrat- und Fettstoffwechsels ausüben. Neben der Makronährstoffrelation wird postuliert, dass Lebensmittel mit einem geringen Glykämischen Index eine längere Sättigung bewirken können, wodurch sich die Energiezufuhr vermindert und ein Gewichtsverlust resultiert. Im Rahmen des Projektes sollen isoenergetische Formulaprodukte mit unterschiedlicher Betonung von Kohlenhydraten, Fetten und Proteinen im Hinblick auf ihre Effektivität vergleichend untersucht werden.

Methode: Innerhalb einer achtwöchigen, randomisierten Gewichtsreduktionsstudie wurden die Auswirkungen der kohlenhydrat- und proteinbetonten Formuladiäten bei 160 übergewichtigen Frauen und Männern (BMI 27,9–35,1 kg/m^2) untersucht. In den Wochen 1+2 verzehrten die Probanden drei Formulaprodukte pro Tag anstelle der Hauptmahlzeiten. In den Wochen 3+4 erfolgte ein teilweiser Mahlzeitenersatz von zwei Mahlzeiten. Abschließend (Wochen 5-8) ersetzte das Formulaprodukt nur noch eine Hauptmahlzeit. Darüber hinaus wurden in einem Cross-over-Versuch bei 20 gesunden männlichen und weiblichen Probanden der GI sowie die Sättigung beider Produktvarianten bestimmt.

Ergebnisse: Im Rahmen der Gewichtsreduktionsstudie konnten in beiden Gruppen signifikante Senkungen von anthropometrischen Größen, der Körperzusammensetzung, Parametern des Kohlenhydrat- und Lipidstoffwechsels sowie klassischen Entzündungsmarkern festgestellt werden. Des Weiteren zeigte die Studie, dass eine kalorienreduzierte Ernährung das Oxylipinmuster beeinflusst und sich eine Reduktion der Arachidonsäure Metaboliten erzielen lässt. Die proteinreiche Formuladiät kann als Lebensmittel mit einem geringen Glykämischen Index eingestuft werden und die kohlenhydratreiche Formuladiät als Lebensmittel mit einem mittleren Glykämischen Index.

Schlussfolgerung: Sowohl das kohlenhydrat- als auch das proteinbetonte Formulaprodukt erwiesen sich im Hinblick auf die Gewichtsreduktion und die gleichzeitige Verbesserung metabolischer Risikofaktoren bei Übergewicht und Adipositas als gleichwertig. Es lassen sich keine Zusammenhänge zwischen dem Glykämischen Index der Formuladiäten sowie der ausgelösten Sättigung und der Energieaufnahme aufzeigen. Die Relation der Hauptnährstoffe scheint nicht entscheidend für die Effektivität der Formulaprodukte und die unterschiedlichen diätetischen Möglichkeiten zur Gewichtsreduktion, erlauben eine Berücksichtigung der individuellen Ernährungsgewohnheiten. Es sind weitere Studien notwendig, die den genauen Aspekt der Nahrungs- und Energieaufnahme untersuchen, um die Vorteile der Makronährstoffe innerhalb der Gewichtsreduktion zu ermitteln.

Trial Registrierung: German Clinical Trials Register DRKS00005481

Schlagwörter: Kohlenhydrate, Proteine, Formuladiät, Gewichtsreduktion, metabolische Risikofaktoren, Glykämischer Index

List of Papers

This thesis is based on the following papers:

Paper I **Efficacy of high carbohydrate versus high protein meal replacements on weight reduction - a randomized controlled trial**. Möller K, Willers J, Hahn A. *J Obes Weight Loss Ther* 2015; 5 (3): 1-9.

Paper II **Effects of a high carbohydrate and high protein formula diet on body composition and metabolic risk parameters in obese subjects.** Möller K, Schneider I, Willers J, Hahn A. *J Obes Weight loss Ther* 2015; 5 (6):1-7

Paper III **Influence of weight reduction on blood levels of C-reactive protein, tumor necrosis factor-α, interleukin-6, and oxylipins in obese subjects.** Möller K, Ostermann AI, Rund K, Thoms S, Blume C, Stahl C, Hahn A, Schebb NH, Schuchardt JP. *PLEFA* 2016; 106: 39-49.

Paper IV **Glycemic index and glycemic load of a carbohydrate-rich and protein-rich formula diet.** Möller K, Willers J, Schneider I, Hahn A. *J Nutr Health Sci* 2015; 2 (4): 406

Table of Contents

Figures

Tables

Abbreviations

AA	Arachidonic acid
ALA	α-linolenic acid
ANOVA	Analysis of variance
BCM	Body cell mass
BFM	Body fat mass
BMI	Body Mass Index
COX	Cyclooxygenase
CVD	Cardiovascular disease
CYP	Cytochrome P450
DBP	Diastolic blood pressure
DGLA	Dihomo-γ-linolenic acid
DHA	Docosahexaenoic acid
DiHDPE	Dihydroxydocosapentaenoic acid
DiHETE	Dihydroxyeicosatetraenoic acid
DiHODE	Dihydroxyoctadecadienoic acid
DiHOME	Dihydroxyoctadecenoic acid
ECM	Extracellular mass
EKODE	Epoxyketooctadecenoic acid
EPA	Eicosapentaenoic acid
EpDPE	Epoxydocosapentaenoic acid
EpOME	Epoxyoctadecenoic acid
GI	Glycemic Index
GL	Glycemic Load
HC	High carbohydrate formula diet
HDL-C	High-density lipoprotein
HDHA	Hydroxydocosahexaenoic acid
HEPE	Hydroxyeicosapentaenoic acid
HETE	Hydroxyeicosatetraenoic acid
HipC	Hip circumference
HODE	Hydroxyoctadecadienoic acid
HOMA-IR	Homeostasis model assessment for insulin resistance
HP	high protein formula diet
hsCRP	high-sensitivity C-reactive protein
IAUC	Incremental Area under the Curve
IL-6	Interleukin-6
LA	Linoleic acid
LCD	Low calorie diet
LDL-C	Low-density lipoprotein cholesterol

LOX	Lipoxygenase
MetS	Metabolic syndrome
mITT	Modified intention to treat
oxo-ETE	Oxo-eicosatetraenoic acid
oxo-ODE	Oxo-octadecadienoic acid
SBP	Systolic blood pressure
SD	Standard deviation
SE	Standard error
TAG	Triacylglycerol
TC	Total cholesterol
TNF-α	Tumor necrosis factor-α
TriHOME	Trihydroxyoctadecenoic acid
TW	Total body water
VAS	Visual Analogue Scale
VLCD	Very low calorie diet
VLDL	Very low-density lipoproteins
WC	Waist circumference
WHR	Waist-to-hip-ratio

1. General Introduction

1.1 The global epidemic of obesity

"We must eat to stay alive but we do not live for the sake of eating" stated the Greek philosopher Heraklit 2.500 years ago. During millions of years of human evolution this was applied for the majority of people in developing countries, while gain of weight was difficult to obtain. In the late 18th century people of developed countries are continuing the struggle to survive with a minimum amount of food. Solutions to remove these problems consisted of adding sugar and fat to the diet for increasing energy intake [Caballero 2007].

However, this perspective has changed and eating became increasingly apparent for numerous reasons than only for survival. Next to the excess of food due to industrialization, the life style has changed and initial physical work reduced. These conditions result in an imbalance between energy intake and energy expenditure, which caused excessive accumulation of adipose tissue [Malik et al. 2012]. This occurrence enhanced the development of overweight as well as obesity in global epidemic dimensions. In the 1930´s the link between obesity and impaired health has been considered as a problem for the first time. Currently, the proportion of overweight and obese persons in developed but also in developing countries is increasing. In 2000, a historical change has been reached: The number of overweight people exceeds the number of underweight people [Gardner and Halweil 2000, Popkin et al. 2012].

Today, overweight and obesity have become a major public health problem. Obesity is defined as a condition of abnormal or excessive fat accumulation that impairs health. Body Mass Index (BMI) is a typical classifier, whereby BMI from 25-29.9 kg/m^2 is defined as overweight and BMI ≥ 30 kg/m^2 as obese [WHO 2015b] . According to the World Health Organization 2015 (WHO), there are more than 1.9 billion overweight adults worldwide and 600 million of these adults are obese [WHO 2015b]. A recent systematic review focusing on obesity among European adults demonstrate that the prevalence of obesity in men range from 4.0-28.3% and in women from 6.2-36.5%. Here are considerable geographic variation, with prevalence rates in Central, Eastern, and Southern Europe being higher than those in Western and Northern Europe (**Figure 1**) [Berghöfer et al. 2008]. Considering data from 2008 to 2011 for German adults, the prevalence of overweight was 67.1% in men and 53.0% in women and the prevalence of obesity was 23.3% in men and 23.9% in women [Mensink et al. 2013].

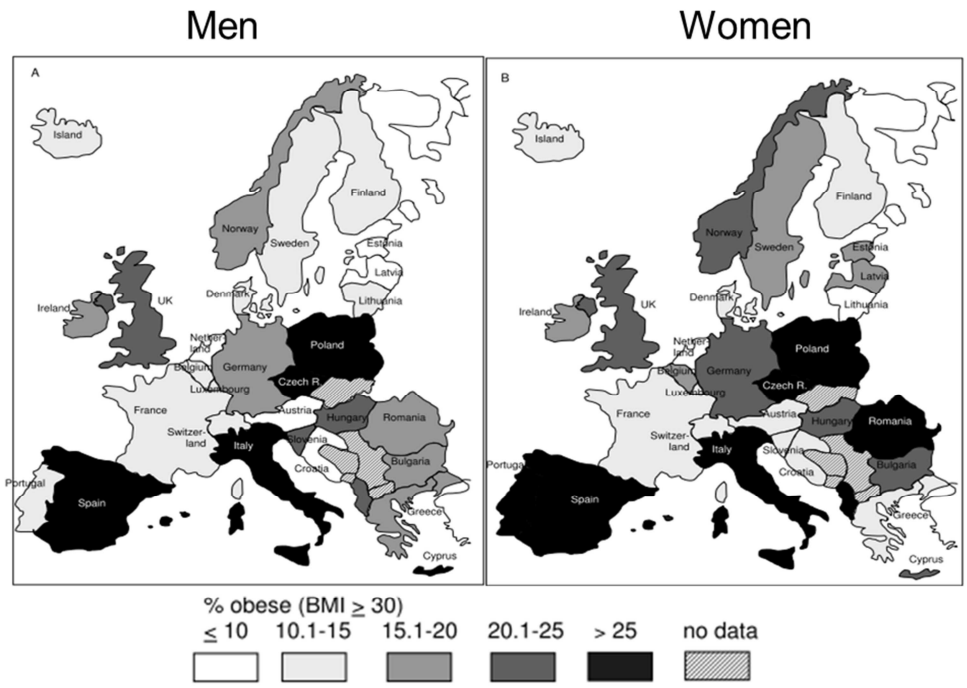

Figure 1: Prevalence of obesity (BMI >30 kg/m^2) among men and women in Europe [Berghöfer et al. 2008].

1.1.1 Contributing factors of obesity

Obesity is the foremost cause of chronic diseases in the world, which is undoubtedly of multifactorial origin. Basically, it can be taken as given that body weight gain and adipose tissue accumulation result from a positive energy balance [Malik et al. 2012, Crino et al. 2015]. The imbalance between energy intake and energy output is due the following factors, which are shown in **Figure 2**.

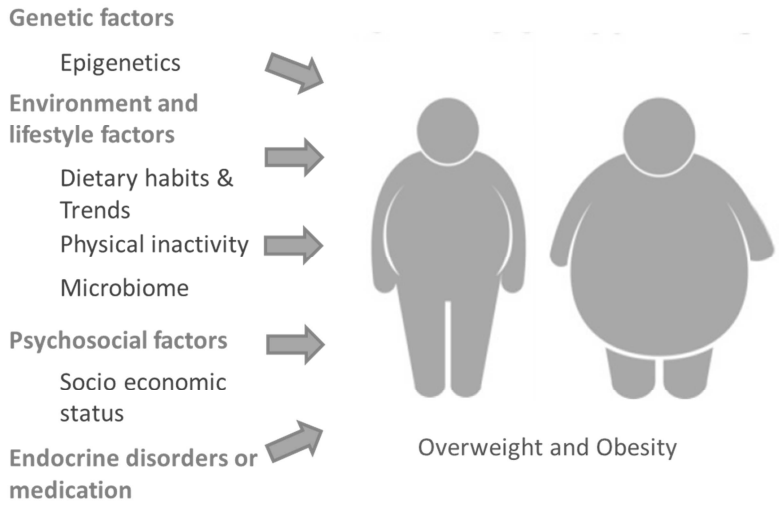

Figure 2: Contributing factors of overweight and obesity

(Epi)- genetic factors

Since obesity research started, several contributing factors on obesity development have been discovered. The genetic determinant has intensely studied in the past decades and is associated with influences on body fat mass (BFM) distribution, energy expenditure and metabolism [Tchernof and Despres 2013]. Studies propose that genetic factors cause 51% of variation in visceral adipose tissue accumulation [Bouchard 1997]. This is supported by twin studies, which induced weight gain by overfeeding. The results demonstrated BFM distribution varied widely among the twin pairs but within each of them was a less difference in fat distribution and visceral fat accumulation [Bouchard 1990]. In recent years, a large number of genes have been applied to be involved in the development of monogenic and polygenic obesity disorders. Monogenic obesity disorders occur rarely and based on defects of individual genes e.g., leptin [Montague et al. 1997], leptin receptor [Clément et al. 1998], melanocortin 4 receptor [Vaisse et al. 1998] or proopiomelanocortin [Krude et al. 1998]. The genes are involved in the leptin-melanocortin system, which is crucial for satiety and energy balance [Razquin et al. 2011]. In most cases obesity has a polygenic background including polymorphisms on several genes. In genome-wide association studies, previously 58 gene variants have been associated with adiposity levels and different biological pathways (e.g., substrate utilization or thermogenesis) [Moustafa and Froguel 2013, Lu and Loos 2013].

Environmental and lifestyle factors

During the evolution, there has been a dramatic dietary change. Today, the western diet has especially changed the macronutrient and fatty acid composition, the glycemic load and fiber content as well as the micronutrient density compared to our diet 10.000 years ago [Cordain et al. 2005]. This progression to modern diets during the past decade might be responsible for promoting chronic diseases, like obesity, diabetes atherosclerosis, hypertension or different forms of cancer in our current society [Jew et al. 2009,Carrera-Bastos et al. 2011]. These changes in dietary composition happened simultaneously with the increasing prevalence of obesity. Around 1900, the energy contribution from carbohydrates and fat estimated to be 60-70% and 20-25%, respectively. By contrast, current diets contain about 30-35% of total calories from fat, whereas 50-55% of calories are derived from carbohydrates, which consist of more processed and highly refined food products [Caballero 2007, Jew et al. 2009]. The WHO lists dietary factors as a major contributor influencing the imbalance between energy intake and energy output [WHO 2015b]. There is growing body of evidence that changing dietary macronutrient composition of diet (i.e., carbohydrates, fats and protein) could play a role in weight gain [Hall et al. 2011].

An important part in the development of overweight and obesity has been assigned to high consumptions of sugar-rich soft drinks, refined high glycemic index carbohydrates and high animal fat and protein [Malik et al. 2012, Astrup et al. 2014], whereas whole grain and low-glycemic index carbohydrates may decrease the risk of weight gain [Du et al. 2010, Jebb 2015]. Carbohydrates generally can be separates into fiber and sugar. Several studies indicate, that sugar [Fogelholm et al. 2012, Song et al. 2012, Te Morenga et al. 2012] and a reduced fiber intake, caused by processed food composition, is strongly involved in weight gain [Popkin 2004, Moubarac et al. 2013]. Further studies suggested evidence that diets high in fat enhance weight gain, which obviously relates to the high energy density of fat compared to carbohydrates and proteins [Swinburn et al. 2004, Fogelholm et al. 2012]. Currently, the protein content in a diet neither associates with weight gain [Lejeune et al. 2005, Westerterp-Plantenga et al. 2012,] nor is a determinant of the prevalence of obesity [Fogelholm et al. 2012, Crino et al. 2015].

Low-cost and processed food products and the increased addiction on prepared food, which is often nutrient poor, are suggested to influence the unbalanced energy equation in obesity [Caballero 2007]. Studies indicate that higher energy intake is associated with larger increase of waist circumferences and body weight [Du et al. 2009,Romaguera et al. 2010]. The consumption of processed food products is related to high energy density by high levels of fats and sugars [Davey 2004, Howarth et al. 2006, Kearney 2010]. The evidence for environmental and lifestyle factors that might promote overweight and obesity is shown in **Table 1**.

Factors like physical inactivity also influence the obesity development. In particular advances in technology and transportation have reduced the need for physical activity in daily life. Many people of our population live a sedentary life, while they spend hours in front of television, electronic games and computers [Andersen et al. 1998]. In addition, the gastrointestinal tracts also play an important role in the regulation of food intake and energy balance. The gut microbiota has been recently suggested to be an environmental factor involved in body weight control and influences eating behavior and glucose homeostasis [Small and Bloom 2004, Näslund and Hellström 2007, Ley 2010]. The interactions between microbes in the gut may affect fat accumulation, insulin resistance, insulin sensitivity and inflammation in animal models [Bäckhed et al. 2004, Bäckhed et al. 2007, Gregor and Hotamisligil 2011].

Table 1: Environmental and lifestyle factors, which might promote the risk of obesity. In accordance with Swinburn et al. 2004

Evidence	Decreases risk of obesity	No relationship	Increases risk of obesity
Convincing	▪ Regular physical activity ▪ High fiber intake		▪ Sedentary lifestyles
Probable	▪ Healthy food choice for children ▪ Breastfeeding		▪ High intake of energy dense foods ▪ Heavy marketing of energy dense foods and fast food ▪ Adverse social and economic conditions ▪ High sugar drinks
Possible	▪ Low GIycemic Index foods	▪ Protein content of the diet	▪ Large portion sizes of food prepared outside the home ▪ Rigid restraint/periodic disinhibition' eating patterns
Insufficient	▪ Increased eating frequency		▪ Alcohol

Psychosocial and secondary factors

Earlier studies suggested, that psychological and behavioral factors are responsible for increasing the prevalence of obesity [Wadden et al. 2002]. Today, those factors play a subordinate role for development of obesity, although some obese individuals have an increased food intake due to emotional stress (e.g., to drown sorrow or isolation). Nowadays, social and socioeconomic factors are the most important. Studies have shown a social gradient: the lower the value of socioeconomic status, the higher body size [McLaren 2007].

Secondary causes of obesity include endocrine disorders (e.g., cushing syndrome, hypothyroidism) or intake of medication (e.g., antidiabetics, antidepressants or anto-psychotics).

1.1.2 Obesity-related metabolic disorders

Historically, the accumulation of fat mass during positive energy balance is useful for surviving periods of reduced food intake. The excessive caloric intake may exceed the oxidative capacity and in contrast to the store of carbohydrates in form of glycogen for short-term energy provision, the storage capacity for fat as triacylglycerol (TAG) is limited [Boden et al. 1994, Roden et al. 1996]. The presence of an impaired lipid storage capacity of adipose

tissue will lead to lipid accumulation in non-adipose tissue [van der Zijl et al. 2011]. This results in ectopic lipid accumulation in organs such as the liver, pancreas, skeletal muscle and heart as well as increased formation of visceral fat tissue, which disrupt metabolic processes and impairs organ function [van der Zijl et al. 2011, Snel et al. 2012]. Due to the excess of caloric intake, this storage capacity has developed a pathogenesis mechanism, which is associated with various health risks [Tchernof and Despres 2013, Martinez et al. 2014].

Body weight gain is stated as a major risk factor for nutrition-related non-communicable diseases, including metabolic diseases like hypertension, type 2 diabetes, chronic inflammation, cardiovascular diseases or certain forms of cancer [WHO 2015b, Rodríguez-Hernández et al. 2013]. Obesity is one of the leading global risks for mortality worldwide [Blundell and Macdiarmid 1997, Global Health Risks Report 2009]. Metabolic disorders including elevated levels of glucose, insulin resistance, hyperlipidemia and low-grade inflammation are normally evident in obese subjects [Eckel et al. 2005, Rodríguez-Hernández et al. 2013, Jung and Choi 2014].

1.1.2.1 Glucose intolerance, hyperinsulinemia and dyslipidemia

The harmful effects of abdominal obesity are largely explained by the visceral adipose tissue depot. Studies demonstrated that visceral adipose tissue accumulation is an independent risk factor associated with insulin resistance, type 2 diabetes, dyslipidemia, liver fattening, cardiovascular disease, and all-cause mortality [Després 1998, Kuk et al. 2006, Trujillo and Scherer 2006, Smith et al. 2012, Britton et al. 2013]. Adipose tissue has been recognized as a main storage of excess energy derived from food intake and acts as endocrine organ by secreting various hormones and cytokines, which are important regulators of glucose and lipid homeostasis [Kershaw and Flier 2004]. Metabolic disturbances in obesity related to a dysfunctional adipose tissue lead to impaired secretion of cytokines, deranged glucose and lipid metabolism, elevated hepatic triglyceride and an increase lipolysis.

The increase of free fatty acid (FFA) levels and inflammatory cytokines plays a specific role in development of hepatic or skeletal insulin resistance, which usually means resistance to the effects of insulin on glucose uptake, metabolism, or storage [Kahn and Flier 2000]. FFA are taken up by protein-mediated membrane transport (CD36, fatty acid transport), along with passive diffusional uptake [Snel et al. 2012]. The excessive rise of FFA in skeletal muscle cell may exceed the mitochondrial oxidative capacity and levels of fatty acid metabolites such as fatty acyl-CoA and diacylglycerol increase [Huffman et al. 2009]. These metabolites activate a serine/threonine kinase cascade, such as protein kinase C, leading to phosphorylation of insulin receptor substrate (IRS) 1 on serin residues. Phosphorylated

forms of IRS cannot activate phosphatiddyl-inositol-3-kinase (PI3K), which in turn results in a decreased glucose transporter 4 (GLUT 4) regulated glucose uptake [Shulman 2000].

An increase of fatty acids metabolites in hepatic cells leads to activation of protein kinase C (PKC), which inhibits the function of IRS 2 such that insulin binding no longer activates insulin receptor signal transduction to trigger glucose uptake by GLUT 2 or glycogen synthase activity [Snel et al. 2012]. Furthermore, the phosphorylated IRS and PI3K results in impaired insulin-suppressed hepatic glucose production, which contributes to increased plasma glucose levels [Reaven 1988, Boden and Schulman 2002, Ezquerra et al. 2008]. In addition to stimulating gluconeogenesis, elevate FFA also affect hepatic insulin clearance and insulin secretion in the long-term, which results in hyperinsulinemia [Boden and Schulman 2002]. Finally, insulin resistance in obesity is manifests by failed beta cells of the pancreas caused by FFA and hyperglycemia in the long run, which contributes the development of type 2 diabetes [Kahn et al. 2006, Robertson et al. 2007, Cerf 2013].

Moreover, obesity is associated with an increased prevalence of dyslipidemia. The dyslipidemia of obesity is characterized by an abnormal amount of lipids including raised levels of FFA and TAG concentrations, increased low-density lipoprotein cholesterol particles (LDL-C) as well as reduced high-density lipoprotein cholesterol (HDL-C) concentrations [Jung and Choi 2014]. The most important explanation for the adverse effects of visceral obesity is the increased delivery of FFA from the visceral depot, through lipolysis, to the liver via the portal vein. This leading to elevated hepatic TAG production as very low-density lipoproteins (VLDL), which promotes hypertriglyceridemia [Jung and Choi 2014, Adiels et al. 2008]. Thus, a cholesteryl ester transfer of TAG for cholesterol esters between TAG-rich VLDL and lipoproteins occurs, which are relatively richer in cholesterol esters (LDL-C, HDL-C). This leads to a decreased HDL-C concentration and an increase TAG content in LDL, which is a prefer substrate for hepatic lipase [Adiels et al. 2008]. The increase lipolysis of TAG-rich LDL-C particles results in the formation of small dense LDL, which is associated with a higher risk of cardiovascular diseases [Klop et al. 2013, Chan et al. 2013]. The added risk of atherosclerosis associated with postprandial lipids could relate to the increase in TAG-rich lipoprotein levels, including chylomicrons, chylomicron remnants and VLDL and lipolysis products [Alipour et al. 2008, Adiels et al. 2008]. The mechanism of obesity induced disorders is visualized in **Figure 3**.

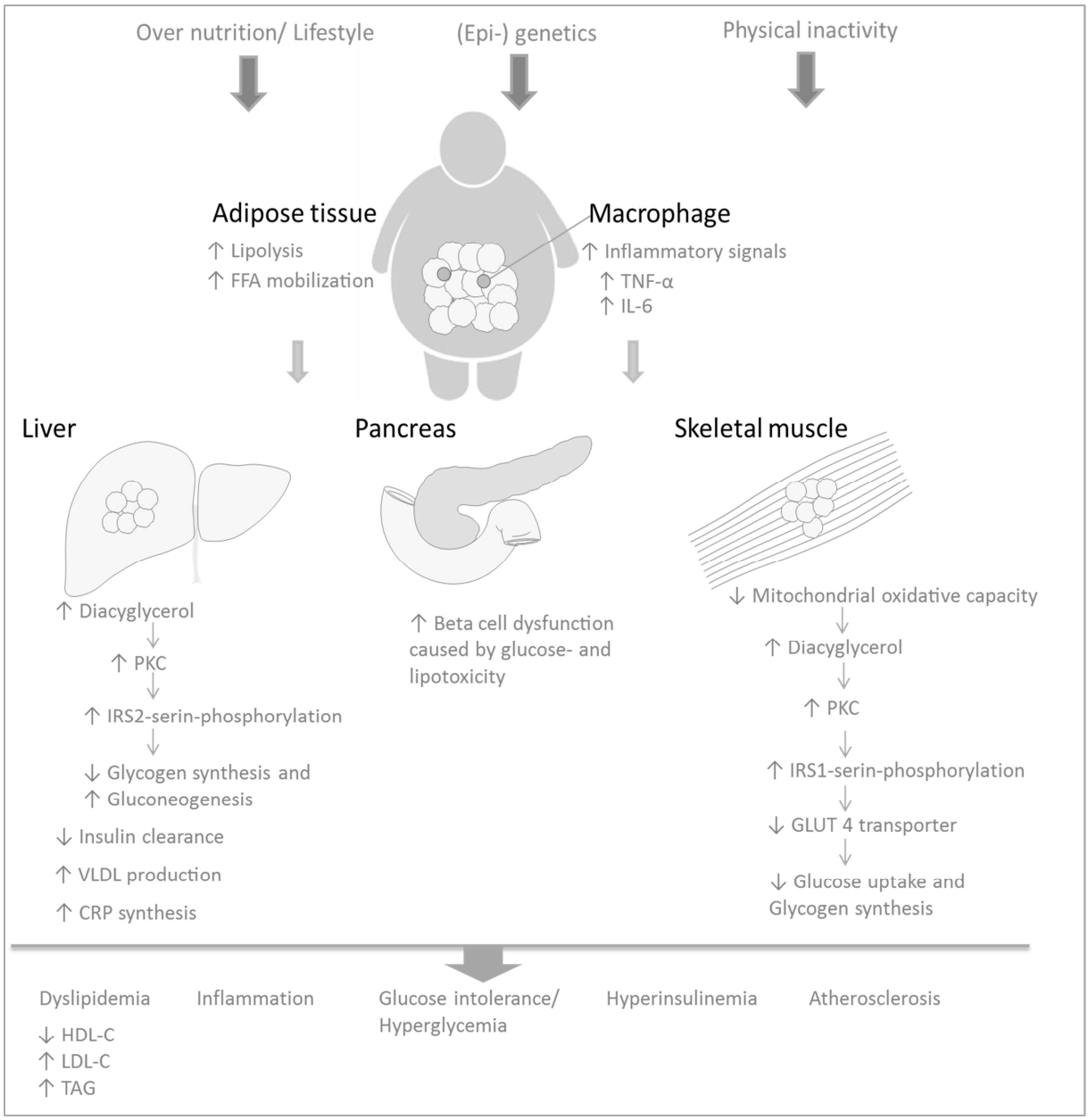

Figure 3: Obesity-related metabolic disorders

CRP: C-reactive protein, HDL-C: high-density lipoprotein-cholesterol, IL-6: interleukin 6, IRS: insulin receptor substrate, LDL-C: low-density lipoprotein-cholesterol, PKC: protein kinase, TNF-α: tumor necrosis factor alpha, VLDL: very low-density lipoprotein. The Figure was designed in accordance with Shulman 2000, Adiels et al. 2008, van Greevenbroek et al. 2013 and Snel et al. 2014.

1.1.2.2 Low-grade inflammation

Obesity has been linked to chronic low-grade inflammation, which is proposed to have a crucial role in the development of metabolic disorders including insulin resistance, type 2 diabetes, fatty liver disease and cardiovascular disease [Hotamisligil and Erbay 2008]. An increased infiltration of macrophages caused by secretion of monocyte chemoattractant protein-1 (MCP-1) in adipose tissue activates pro-inflammatory serine kinase cascade

signaling pathways, resulting in secretion of pro-inflammatory tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) [Ferrante 2007, van Greevenbroek et al. 2013, Choi et al. 2013]. The abnormal expression of the pro-inflammatory cytokine TNF-α in adipose tissue exerts numerous effects of insulin [Emanuela et al. 2012]. There is evidence that TNF-α promotes insulin resistance by the inhibition of the IRS 1 signaling pathway [Hotamisligil et al. 1995]. Further studies demonstrated, that a high fat diet elevate TNF-α production in people with high BMI [Morin et al. 1997].

IL-6 is a pro-inflammatory cytokine produced by many different cell types, such as immune cells and adipose tissue that has an important role in regulation of energy homeostasis and inflammation [Fernandez-Real 2001]. The IL-6 receptor is expressed in several regions of the brain controlling appetite and energy intake [Stenlöf et al. 2003]. Further studies demonstrated a positive association between obesity and plasma IL-6 levels in men and women [Vgontzas et al. 1997, Roytblat et al. 2000, Straub et al. 2000].

TNF-α and IL-6 in turn are both stimulators of C-reactive protein (CRP) release from hepatocytes [Nicklas et al. 2005, Choi et al. 2013], which also trigger chronic low-grade inflammation. Levels of hsCRP ≥ 3 mg/L (High-sensitivity C-reactive protein) are useful for classification to asses inflammation state [Ridker and Cook 2004, Ridker 2007]. Therefore, higher levels of hsCRP, IL-6 and TNF-α indicate an inflammatory state in obese subjects [Hotamisligil et al. 1993, Pickup et al. 1997, Visser 1999, Choi et al. 2013], which playing an important role in atherosclerotic processes [Emanuela et al. 2012]. Studies showed that elevated circulating concentrations of pro-inflammatory cytokines predict the development of insulin resistance and other metabolic complications of obesity [Libby 2002, Vidyasagar et al. 2013, Chen et al. 2015].

In addition, elevated levels of oxidized polyunsaturated fatty acids (PUFA), the oxylipins, are related to obesity [Pickens et al. 2015, Lieb et al. 2014]. The dietary FA intake shifts in obesity [Ramsden et al. 2012], which changing the FA composition of cellular phospholipid membranes and plasma phospholipid [Hulbert et al. 2005, Zong et al. 2012]. PUFAs within membrane phospholipid serve as substrates for the biosynthesis of oxygenated FA metabolites through either enzymatic or non-enzymatic pathways and only limited information is available about the biological role of several hydroxy, epoxy and dihydroxy FAs derived from AA and other PUFAs such as linoleic acid (LA 18:2n-6), dihomo-γ-linolenic acid (DGLA 20:3n-6), α-linolenic acid (ALA 18:3n-3), eicosapentaenoic acid (EPA 20:5n-3) or docosahexaenoic acid (DHA 22:6n-3) [Powell and Rokach 2015]. Especially, 5-Lipoxygenases (LOX) products of AA (e.g., 5-hydroxyeicosatetraenoic acid (5-HETE) or 5-oxo-eicosatetraenoic acid (5-oxo-ETE)) affect inflammation by increasing the production of pro-inflammatory cytokines and inducing chemotaxis to attract inflammatory cells in the blood

vessels [Horrillo et al. 2010, Poeckel and Funk 2010]. The enzyme 12-LOX is involved in the production of pro-inflammatory AA-derived oxylipins (e.g., 12-HETE) [Powell and Rokach 2015]. 12-LOX are assumed to play a direct role in obesity-related inflammation and the pathology of insulin resistance [Nunemaker et al. 2008, Sears et al. 2009, Dobrian et al. 2011]. Therefore, obesity induced changes in metabolism or oxidized hydroxy, epoxy and dihydroxy FA levels will greatly affect the character of the inflammatory response [Pickens et al. 2015].

1.1.2.3 Metabolic Syndrome

The metabolic syndrome (MetS) is a cluster of obesity-related metabolic and cardiovascular risk factors presented in Figure 3. MetS is defined in various ways, but the essential components that relate to atherosclerosis and cardiovascular diseases are the following [Ervin 2009, Alberti et al. 2009, Kaur 2014]:

- Abdominal obesity,
- Hyperglycemia,
- Insulin resistance,
- Dyslipidemia (elevated TAG levels, small LDL particles, low HDL-C)
- Hypertension,
- Prothrombotic state,
- Proinflammatory state.

A diagnosis of the MetS is made when elevated measurements of three or more of the following risk factors are present: waist circumferences (WC), fasting blood glucose, blood pressure, HDL-C and TAG [Alberti et al. 2009]. The prevalence of MetS is rising and high in all western societies, probably as a result of the obesity epidemic [Kassi et al. 2011, Hollman and Kristenson 2008]. Approximately between 15% and 34% of the population in Europe and America are believed to have the MetS [Nonogaki et al. 2003, Hillier 2005, Hollman and Kristenson 2008, Ervin 2009].

Effective treatment strategies include diet, exercise, and probably the use of pharmacologic agents to handle specific risk factors. Especially weight loss might significantly improve all aspects of MetS. Dietary intervention is appropriate for addressing different aspects of the MetS, including reducing of sodium intake to lower blood pressure, reducing intake of foods with high glycemic index to lower TAG levels as well as lower saturated fat intake to lower insulin resistance [Deen 2004].

1.2 Treatment of obesity

Obesity is a chronic condition that needs lifelong treatments. Recommendations agree that people who are overweight and obese need to be advised and given perspective and practical strategies for weight reduction in daily life [Astrup 2008]. Adapted treatment programs on personal life situations of patients are successful for long-term weight reduction and maintenance. Therefore, individual multimodal approaches to treat obesity are required. The listed treatment goals should be realistic and adapted to the individual situation of the patient [Wirth et al. 2014]:

- Long-term weight reduction:
  - BMI 25 to 35 kg/m^2: >5% of initial weight
  - BMI > 35 kg/m^2: >10% of initial weight
- Improvement in obesity-related risk factors
- Reduction in obesity-related diseases
- Lowering of risk of early death
- Prevention of inability to work and early retirement
- Reduction of psychosocial disorders
- Improvement of quality of life

According to the guidelines of the German Obesity Association, the foundation for weight management should include the elements of the basic program (diet therapy, exercise therapy and behavioral modification) [Wirth et al. 2014]. If necessary, the treatment can be extended by drug therapy and/or surgical interventions. To reduce body weight and adipose tissue, a recommended diet should lead to a negative energy balance. The aim can be achieved by applying an energy restriction diet, that will produce an energy deficit of about 500 kcal/day, or more in individual cases [Abete et al. 2010, Wirth et al. 2014]. In order to reach these goals, several dietary strategies are available (reduce fat or carbohydrate consumption, reduce both fat and carbohydrate consumption). In addition, the use of formula products supplying 800 to 1200 kcal/day may be considered as therapeutic option. For weight reduction, a stepwise procedure is useful (**Table 2**).

Table 2: Stepwise diet therapy for weight management. In accordance with the guidelines of the German Obesity Association 2007 and 2014.

Level	Concept	Indication
I	▪ Reduction of fat intake to about 60 g/day without limited consumption of carbohydrates (low fat diet)	▪ Weight loss ▪ Long-term stabilization of body weight after weight loss
II	▪ Moderately energy reduced varied diet (low calorie diet) o Limited fat intake o Reduced consumption of carbohydrates and protein ▪ Energy deficit should be about 500 to 800 kcal/day	▪ Standard therapy for weight loss
III	▪ Meal replacement with formula products ▪ One or two main meals per day are replaced by formula products (protein drink or bar, etc.: ca. 200 kcal per meal)	▪ Support of the standard therapy for weight loss
IV	▪ Formula diets ▪ Total use of formula diets with a caloric value of 800 to 1200 kcal/day; limited in time	▪ Initial weight reduction under medical observation

1.2.1 Dietary macronutrient distribution for obesity treatment

Currently, for health advice the WHO recommends that daily energy intake is derived primarily from carbohydrates (55-75%) with less than 10% of energy from free sugars and at least 25 g of fiber. For fat, the WHO recommendation is 15-30% of energy with <10% from saturated fats, and 10-15% of energy from protein [WHO 2015b, Crino et al. 2015].

The major macronutrients contain quite different quantities of energy, whereas 1 g fat contains 9 kcal, the same amount of carbohydrates and proteins contain 4 kcal. This represents averages for metabolizable energy of absorbed macronutrients which are transformed in vivo to substrates that can either be oxidized to produce energy for conducting biological processes or they may be stored [Hall et al. 2012]. Carbohydrates are stored as glycogen in relatively small amounts in liver and skeletal muscle, which is associated with water. The absorbed protein takes many specific forms as body protein and is weakly bonded to water like glycogen. By contrast, lipids in form of TAGs present within adipose tissue are not associated with water and are the largest source of stored energy. Therefore, an imbalance between intake and expenditure of these macronutrients may lead to an alteration in body composition, which has been suggested to play a major role for changes in weight [Hall et al. 2012]. Moreover, obesity is also linked with the MetS and

several chronic diseases. Therefore, it may be of even greater importance that the optimal diet not only decreases body weight but also promotes a metabolic profile associated with reduced risk of developing chronic diseases.

Selecting the optimal composition of macronutrients for a low-calorie meal plan is an important consideration for the initiation and maintenance of weight loss for overweight and obese patients. There is still debate about which diet with different proportion of carbohydrates, lipids and proteins will produce the best outcome on obesity treatment. Therefore, several types of diets have focused on macronutrient compositions in order to affect metabolic targets that are the most effective way to support body weight loss [Skov et al. 1999, Sacks et al. 2009, Fogelholm et al. 2012].

The following part of the thesis describes various dietary approaches to weight loss (i.e., high carbohydrate/low fat diets, low carbohydrate/high fat diets, high protein/low fat diet, low glycemic index diets and formula diets).

1.2.1.1 High carbohydrate / low fat diet

Low fat diets with relatively high carbohydrate and moderate protein content have been advocated for weight loss for many years [Freedman et al. 2001, Strychar 2006, Abete et al. 2006]. The basis of these diets is primarily related to the lower energy density and the prevention of overeating. In general, such diet approaches are energy reduced (deficit of 500 – 1000 kcal/day), low in fat (<30% of energy intake) and high in carbohydrate (55 - 60% of total daily energy intake) [Freedman et al. 2001]. Studies suggested that high energy density of fat compared to carbohydrates and proteins is more fattening and promotes weight gain [Astrup et al. 2002, Fogelholm et al. 2012, Swinburn et al. 2004].

The low fat approach has been further attributes with high carbohydrate content, which are based primarily on the intake of vegetables, whole grain, fruits, beans, non-fat dairy products and lower amounts of white flour, sugar and animal protein [Abete et al. 2006]. Studies indicates that this strategy of consuming more complex carbohydrates and higher fiber foods are associated with lower energy intake [Swinburn et al. 2004] which enables individuals to eat as much as they want without apparent hunger [Freedman et al. 2001]. Therefore, low calorie diets with high carbohydrate content induce satiety response and decrease hunger [Freedman et al. 2001, Due et al. 2008].

Well known diets in this category include the Dietary Approaches to Stop Hypertension (DASH diet) [Appel et al. 2006, Dickinson et al. 2006], the National Cholesterol Education Program (NCEP) Step I Diet [Yu-Poth et al. 1999, Grundy 2004] and some commercial weight loss programs (e.g., Weight Watchers) [Dansinger et al. 2005]. Numerous

randomized controlled trials assess the effectiveness of low fat, high carbohydrate diets for reducing body weight and improving comorbidities of obesity [Yu-Poth et al. 1999, Hession et al. 2009, Johansson et al. 2013]. Evidence supports that high carbohydrate diets with a 10% reduction in dietary fat is induced to obtain a 4-5 kg weight loss in obese people with a BMI of 30 kg/m^2 [Astrup et al. 2002, Abete et al. 2006]. Furthermore, studies reported that higher intake of carbohydrates ensure weight loss [Bradley et al. 2009] and protected against weight regain compared with a control diet with normal macronutrient composition [Due et al. 2008]. In addition to weight loss, low fat diets are lowering the amount of abdominal fat, as shown in reduction of waist circumferences [Strychar 2006] and reduce LDL-C levels [Yu-Poth et al. 1999]. Related to their potential to induce weight loss and waist circumferences, the effects of a high carbohydrate and low fat diet on metabolic derangements are of particular interest. Therefore, consuming a high carbohydrate low fat diet is effectively to reduce TC, LDL-C, insulin secretion and pro inflammatory cytokines, which are considered factors in the development of the MetS [Bradley et al. 2009, Bradley et al. 2009, Poppitt et al. 2002]. Otherwise, high consumption of a simple carbohydrate diet (e.g., highly refined starches and sugar) may have adverse effects on the metabolic risk profile by increasing TAG concentrations and effect no improvements of body weight [Noakes et al. 2005, Poppitt et al. 2002].

Next to the energy-restricted strategies, the high carbohydrate, low fat approach has been also applied in *ad libitum* protocols [Skov et al. 1999, McManus et al. 2001, Astrup et al. 2002, Jebb 2015]. A meta-analysis of 16 trials with a duration of 1-12 month reported that low fat diets without energy restriction resulted in greater weight loss (3.2 kg, $p<0.001$) compared with *ad libitum* usual or medium fat intake [Astrup et al. 2000]. However, the adherence to an energy controlled diet appears to be a large barrier to the long term success of weight maintenance [Makris and Foster 2011]. Study results suggest that a low fat, high carbohydrate diet intervention reduces weight regain at two year follow-up, but this process may be improved by adherence to a reduced fat intake [Swinburn et al. 2001].

Nevertheless, these findings suggest that such diets based on moderate fat intakes, which include mainly monounsaturated and polyunsaturated fats as well as complex carbohydrate and fiber being safe and effective for weight loss and improving cardiovascular risk profile [Makris and Foster 2011].

1.2.1.2 Low carbohydrate / high fat diet

Following the initial interest for diets with high carbohydrate and low fat content, low carbohydrate diets have been popularized, mainly by Dr. Atkins, with regard to be an alternative in the nutritional treatment of obesity [Dansinger et al. 2005]. These diets are

generally referred to low carbohydrate diets, which often consist of limited amounts of carbohydrate (<30% energy per day), while the content of fat is usually about 45 to 65% of daily energy intake [Abete et al. 2006, Makris and Foster 2011]. The low carbohydrate/ high fat diet approach includes consumption of foods that do not contain carbohydrates like meat, fish, poultry, butter or oil and allows controlled amounts of nutrient dense carbohydrate foods (e.g., whole grain products, low glycemic index vegetables) [McAuley et al. 2005].

The possible mechanisms responsible for reduced energy intake induced by low carbohydrate diet with unrestricted fat and protein consumption may be potentially attributed to the higher intake of protein. Protein plays a role in limiting food intake by changes of satiety factors or other mediators that affect appetite and dietary adherence [Foster et al. 2003, Abete et al. 2006, Weigle et al. 2005]. Short-term studies suggest that individuals consumed greater quantities of protein and freely reduced their food intake during a low carbohydrate diet [Volek et al. 2000]. It is further presumed that reduced energy intake can be related to the monotony of the diet, because choices of food are limited by the requirements of minimizing carbohydrates intake [Brehm et al. 2003, Johnstone et al. 2008]. The restriction of carbohydrates induces fat mobilization, which increases levels of ketone bodies [Scharrer 1999, Johnstone et al. 2008]. In this condition, the blood glucose and insulin levels are reduced, which may also suppress appetite [Bravata et al. 2003, Johnstone et al. 2008]. However, doubts also have been expressed that diets with protein from animal sources are often high in saturated fat, which have a tendency to increase risk of cardiovascular disease (CVD) [Foo et al. 2009, Lagiou et al. 2012].

Many studies indicate low carbohydrate diets can be preferred for rapid weight loss and beneficial metabolic changes [Brehm et al. 2003, Foster et al. 2003, Dansinger et al. 2005, McAuley et al. 2005, Nordmann et al. 2006]. One randomized clinical trial compared the effectiveness of three popular approaches for weight loss and one diet based on national guidelines: (1) Atkins (20-50g carbohydrates/day), (2) Ornish (very high carbohydrate intake, maximum 10% fat), (3) Zone (40% carbohydrates, 30% fat, 30% protein), (4) Learn (Lifestyle, Exercise, Attitudes, Relationships, and Nutrition (55-60% carbohydrates based in national guidelines)) [Gardner et al. 2007]. 311 overweight and obese premenopausal women were randomly assigned to follow one of these four diets for 12 month. The Atkins diet group lost more weight and shown more favorable metabolic effects than the other three groups (–4.7 kg Atkins, versus –2.6 kg Ornish, –1.6 kg Zone and –2.6 kg Learn). In accordance with the results of other short-term studies, no adverse effects and improvements of the CVD risks were observed following the low carbohydrate/ high fat diet [Foster et al. 2003, Abete et al. 2010, Hession et al. 2009]. However, it could not establish whether the increased weight loss and reduced CVD risk is due to the reduced carbohydrate

content or the increased amount of protein [Gardner et al. 2007, Martinez et al. 2014]. In fact, the restrictions of carbohydrates ensure a great weight reduction within the first days, but much of this weight is a loss of glycogen and protein, which are accompanied by a reduction of water and minerals [Abete et al. 2006]. The safety and efficacy of low carbohydrate diets is debated and has been demonstrated in a systematic review [Bravata et al. 2003]. Particular use for longer than 90 days, diets with 20g/day or less of carbohydrates or among participants older than 50 years is insufficient evidence to make recommendations for or against the use of low carbohydrate diets [Bravata et al. 2003]. There are also results of studies with longer duration available. These studies demonstrated no differences in weight loss between low carbohydrate/ high fat and high carbohydrate/ low fat diets at one year [Stern et al. 2004, McAuley et al. 2005, Dansinger et al. 2005] or two years [Sacks et al. 2009, Kerksick et al. 2010]. This suggests that a longer intake of lower carbohydrates may be more difficult to sustain than a lower fat consumption, which may establish no differences in weight loss at one or two years [Makris and Foster 2011].

1.2.1.3 High protein / low fat diet

During the last decade numerous studies have been published on the effects of high protein diets with an emphasis on carbohydrate restriction. Results indicate that high protein diets in combination with controlled energy may present an effective and practical weight loss strategy in overweight or obese subjects [Lee et al. 2009, Noakes et al. 2005, Brehm et al. 2003, Layman et al. 2009]. The protein intake followed a high protein diet is not accurately defined, but protein intake of >25% total energy or 1.6 g protein per day of body weight can be considered as high [Makris and Foster 2011]. A well-known high protein diet provides the Zone diet (40% carbohydrates, 30% fat, 30% protein), which differs mainly from the low carbohydrate and high fat diet (e.g., Atkins diet) because it is typically low in fat. It has been suggested, that macronutrients have been different in their effects on satiety. Protein is related to have a bigger effect on satiety than carbohydrate, which in turn has a higher impact than fat [Hall et al. 2012]. This may facilitate a reduction in energy consumption under ad libitum diets [Skov et al. 1999]. Moreover, it is suggested that diets high in proteins have the highest and most prolonged thermogenic effect compared to the other macronutrients [Abete et al. 2010], which explains the efficacy of such diets for obesity treatment [Johnston et al. 2002].

These dietary approaches of high protein intake have been proposed to have beneficial effects in weight loss [Clifton et al. 2009, Meckling and Sherfey 2007, McAuley et al. 2006]. Further studies have supported that subjects following a diet higher in protein showed more potential improvements in body compositions (i.e., decreases intraabdominal adipose tissue, in WC, waist-to-hip-ratio, BFM and better maintenance of lean body mass (LBM)) [McAuley

et al. 2006, Wycherley et al. 2012, Layman et al. 2009]. In addition, favorable effects of diets high in protein and low in fat were shown by greater reduction of TAG, TC and LDL-C [Noakes et al. 2005, McAuley et al. 2006, Layman et al. 2009]. Accordingly, pooled data from three 12 week randomized parallel trials demonstrated that TAG levels decrease to a higher extent on a high protein low fat diet (29%) compared to a high carbohydrate low fat diet (17%) [Clifton et al. 2009]. This data suggests that high protein low fat diets may be beneficial for individuals with a risk for dyslipidemia, CVD or MetS.

High protein low fat diets also improve weight maintenance after weight loss [Lejeune et al. 2005, Larsen et al. 2010]. While other studies observed no protection against weight regain through a high protein diet [Delbridge et al. 2009, Dale et al. 2009]. These inconsistent results, in particular for longer studies, compare high protein and high carbohydrate diets on weight loss and body composition may contribute to the poor dietary adherence and inadequate nutrition counseling [Dansinger et al. 2005, Sacks et al. 2009, Larsen et al. 2010, Makris and Foster 2011, Clifton et al. 2014]. For example, Sacks et al. (2009) have shown a reduced adherence level to macronutrient goals after six month, which indicates that subjects have difficulties to maintain macronutrient ratios of the calorie restricted diet [Sacks et al. 2009]. These results of trials comparing diets with different macronutrient distribution suggest that adherence is an important predictor of successful weight loss [Esfahani et al. 2011].

1.2.1.4 Low glycemic index diet

Diets with low glycemic index (GI) focus on increased consumption of slowly absorbed carbohydrates that are associated with low postprandial blood sugar and insulin levels. Carbohydrates have been different ways to raise blood glucose and insulin levels. It is thought, that high GI food causes a high insulin-glucagon ratio, which induces hyperinsulinemia, hypoglycemia, and increases hunger and over-consumption [Brand-Miller et al. 2002]. By contrast, low GI food minimizes postprandial insulin secretion and maintains insulin sensitivity [Flint et al. 2007, Rougemont et al. 2007]. Carbohydrate containing foods are related to white bread or glucose, which both have a GI of 100. Thus, foods with a GI value of 70 or higher are considered as high GI foods, those with a GI between 55 and 69 as medium GI foods and those below 55 are considered as low GI foods [FAO 1998]. The GI depends on various factors such as type of carbohydrates, amount and type of fiber, protein and fat content as well as methods of preparation (e.g., cooking, degree of processing storage) that can affect the GI [Brand et al. 1985, Björck et al. 1994, ISO 2010]. Next to the GI the term Glycemic Load (GL) considers the type of carbohydrate and the amount of carbohydrate consumed [Salmeron et al. 1997].

Consumption of low GI and low GL foods during obesity treatment has been proposed that the glycemic response of foods can potentially affect weight loss [Thomas et al. 2007, Rougemont et al. 2007]. Eating low GI foods or meals with a low GL may simplify weight control since they are associated with increased satiety, which induced energy restriction and are suggested to reduce the risk of CVD and diabetes [McMillan-Price and Brand-Miller 2006, Thomas et al. 2007]. However, a number of studies recommended that low GI diets increase satiety more than high GI foods [Thomas et al. 2007], whereby it is not clear if the effect on appetite affects energy intake sufficiently to be effective for weight management [Pawlak et al. 2002, Ford and Frost 2010, Makris and Foster 2011]. Accordingly, a study of healthy subjects observed no differences in either glucose or insulin response or appetite between the intake of low and high GI foods [Alfenas and Mattes 2005].

Low GI diets are mainly based on amounts of vegetables, legumes, fruits, whole grains [Roberts 2000] and are characterized by high fiber content [Thomas et al. 2007, Abete et al. 2010]. In addition, study results demonstrate that the reduction in body weight followed by a low-GI diet is directly associated with fiber intake [Abete et al. 2008]. During this 8-week energy-restricted period the low-GI diet demonstrates higher weight loss (-7.5 ± 2.9% of initial body weight) than those included in a conventional higher GI diet (-5.3 ± 2.6% of initial body weight). Moreover, participants with different degrees of MetS are randomized to either an energy-restricted (500 kcal/day) low GL diet or a low fat diet. At month three and six, weight loss in the low GL group was higher compared to the low fat group. After one year, the weight loss was similar in both groups, while the reduction of waist circumferences was significantly higher in the low fat group (−3.9 ± 5.3 cm versus −5.8 ± 6.8 cm) [Klemsdal et al. 2010]. In addition, to change of body composition, a study showed that an energy-restricted low GI diet is more effective in controlling glucose and insulin metabolism than a high GI low fat diet [Juanola-Falgarona et al. 2014]. Whereas a few studies found significantly higher weight loss in the low GI or low GL diets, several other studies showed non-significant results of low GI or low GL diets for weight or metabolic risk factors [Heilbronn et al. 2001, Pereira 2004, Sloth et al. 2004, McMillan-Price and Brand-Miller 2006, Sacks et al. 2009]. This suggests that other factors than GI or GL may be important.

Referring long-term advice and effects of GI on weight maintenance, the results of clinical trials are limited and mixed. Larsen et al. demonstrate that a diet with low GI, high protein content prevented weight regain, when compared against a high GI, low protein diet [Larsen et al. 2010]. Accordingly, weight maintenance after initial weight loss is improved by lowering the GI of the diet [Ebbeling et al. 2012]. By contrast, participants who followed a low GI/GL diet or a high GI/GL after they had lost 6% of their initial weight have shown no difference in body weight after four month [Philippou et al. 2009]. However, the independent use of low GI

foods or meals with a low GL are restricted by the GI tables who predict the GI composition of a food but often disregard the context of mixed meals and diets [Abete et al. 2010].

1.2.2 Formula diets for obesity treatment

The term „Formula diets" is usually defined as an industrially manufactured nutrient concentrate, which is enriched with vitamins and minerals. The formula diet is a substitute for one or several whole meals as part of the daily ration with the aim of achieving weight reduction. Formula diets are produced based on soy or milk protein and are mostly available in powder and granule forms. The preparation is made by mixing with water or fat reduced milk and requires no special knowledge of food preparation. Different flavors like cream soups or ready-to-drink shakes offer a certain variety when consuming the product [Leeds 2014].

Regulation of formula diets

According to Art. 14a of German Dietary Regulation (Diätverordnung), formula diet is a „food for an energy-restricted diet for weight reduction", i.e., a dietary food. So far the compositional and labelling requirements for dietary food products are governed at European level by Directive 96/8/EC. These requirements apply for foods used in low energy-restricted diets (800 – 1200 kcal/day) for weight reduction which replace the whole or part of the total daily diet [European Directive No 96/8 1996]. The national implementation is achieved through Art. 14a of the German Dietary Regulation (Diätverordnung) and Annex 17 to this regulation.

The following table summarizes the energy content of products as well as the minimum and maximum levels for proteins, fibers, essential fatty acids, vitamins and minerals:

Table 3: Compositional requirements for foods intended to be used in energy-restricted diets for weight reduction. In accordance to Art. 14a of German Dietary Regulation (Diätverordnung) and Directive 96/8/EC

Energy	Per daily ration: 800 kcal (3360 kJ) – 1200 kcal (5040 kJ) Per portion: 200 kcal (840 kJ) - 400 kcal (1680 kJ)*
Protein	25-50% of the total energy; max. 125 g per daily ration
Fat	<30% of the total energy; at least 4,5 g linoleic acid per daily ratio; at least 1 g linoleic acid per portion
Fiber	10-30 g per daily ration
Vitamins and minerals	**Minimum per daily ration**
Vitamin A	700 µg retinol equivalent
Vitamin D	5 µg
Vitamin E	10 mg tocopherol equivalent
Vitamin C	45 mg
Vitamin B1	1,1 mg
Vitamin B2	1,6 mg
Niacin	18 mg nicotinamide equivalent
Vitamin B6	1,5 mg
Folate	200 µg
Vitamin B12	1,4 µg
Biotin	15 µg
Pantothenic acid	3 mg
Calcium	700 mg
Phosphor	550 mg
Potassium	3100 mg**
Iron	16 mg
Zinc	9,5 mg
Copper	1,1 mg
Iodine	130 µg
Sodium	575 mg
Magnesium	150 mg
Manganese	1 mg
Selenium	55 µg

**after the entry into force of the new Regulation the energy content of the food shall not be less than 200 kcal (840 kJ) and shall not exceed 250 kcal (1046 kJ). ** after the entry into force of the new Regulation the amount of potassium per meal provided by the food shall be at least 500 mg [European Commission 2016 b].*

Furthermore, it is prohibited to promote formula products with potential extent of weight reduction or time needed. Health claims referring to a reduction in the sense of hunger or an increase in the sense of satiety under the condition are subject to approval [Art. 10 (1) European Regulation 1924/ 2006, European Regulation (EU) No 432/ 2012. Independently from Directive 96/8/EC these statements can be used, if they are

a. based on generally accepted scientific evidence and
b. well understood by the average consumer [Art. 10 (1) Regulation (EC) No 1924/2006].

Those claims were included in the list of permitted health claims pursuant to the favorable opinion of the European Food Safety Authority (EFSA) of 2010 [EFSA 2010]. This health claim found that a cause and effect relationship had been established between the consumption of meal replacements in substitution of regular meals and the maintenance of body weight after weight loss and also between the consumption of meal replacements in substitution of regular meals in the context of energy-restricted diets and reduction in body weight. It stated that in order to bear the claims a food should contain a maximum of 250 kcal per serving and comply with specifications laid down in Directive 96/8/EC.

More specifically, in the Annex to Commission Regulation (EU) No 432/2012 establishing the list of permitted Article 13(1) health claims, the following two health claims are authorized:

- "Substituting one daily meal of an energy-restricted diet with a meal replacement contributes to the maintenance of weight after weight loss".
- "Substituting two daily meals of an energy-restricted diet with meal replacements contributes to weight loss" [European Regulation (EU) No 432/2012].

Directive 96/8/EC did not establish requirements for total diet replacement for weight control containing less than 800 kcal (3360 kJ). However, more and more foods intended for the general population have been placed on the market carrying similar statements which are presented as health claims for weight control as defined in Regulation (EC) No 1924/2006 [EFSA 2015b].

Therefore, a new dietetic food regulation 609/2013, adopted in June 2013, will become applicable on July 20, 2016 [European Regulation (EU) No 609/2013]. The new regulation will apply regarding foods intended to be used for total diet replacements for weight control, including foods with very low energy content (<800 kcal/day). The regulation pretends the following rules, which will repeal the complementing Directive 96/8/EC and Directive 2009/39/EC in the next three years [European Commission 2016 a]:

- labels should provide information, which appropriate the use of formula diets and do not indicate the prevention or treatment of human disease,
- general compositional and labelling requirements for total meal replacement products for weight control including very low calorie diets,
- approved substances that may be added to the following categories: vitamins, minerals, amino acids, carnitine and taurine, nucleotides and choline and inositol.

In accordance with European Regulation (EU) No 609/2013, foods presented as a replacement for one or more meals of the daily diet are apply as “normal” foods and should in future be regulated by the general principles and requirements of food law [European Regulation (EU) No 609/2013], that include:

- Regulation (EC) No 178/2002,
- Regulation (EC) No 1925/2006 on the addition of vitamins and minerals and of certain other substances to foods,
- Regulation (EC) No 258/97 concerning novel foods and novel food ingredients,
- Regulation (EU) No 1169/2011 on the provision of food information to consumers,
- Regulation (EC) No 1924/2006 on nutrition and health claims made on foods.

Efficacy of formula diets

The efficacy of formula diets is based on an energy deficit, which occurs when energy intake is less than energy expenditure. Mainly, formula diets containing between 200 and 400 kcal per portion and are used as partial or full meal replacement each day, which enable to create an energy deficit easier than usual with a conventional food-reducing diet with a 500-600 kcal/day deficit [Leeds 2014]. The optimal protein composition is provided to limit LBM loss. Due to the European directives the micronutrient composition of formula diets ensure adequate intake of minerals, trace elements and vitamins. Therefore, the use of formula diets ensures to prevent deficiencies of all micronutrients on a daily basis, which may otherwise occur with a conventional diet below 1000 kcal/day [Leeds 2014]. They are especially suitable for people who have difficulties with losing weight, because formula diet products have customer-friendly features due to the predefined serving size and comparatively low costs [Willers et al. 2012]. Currently, a distinction can be made for formula diet products present in the market:

- products intended for low calorie diets (LCD), which provide an energy intake of 800 kcal (3360 kJ) to 1200 kcal (5040 kJ) per day,

- and products intended for very low calorie diets (VLCD), which normally contain fewer than 800 kcal (3360 kJ) [Leeds 2014].

Partial meal replacement

The use of formula diets as partial meal replacement based on the concept to replace one or two main meals per day by formula products. The third main meal should be selected according to principles of balanced diet, but do not exceed 500 – 600 kcal of energy content [Hauner et al. 2007]. Therefore, they may contribute to a total energy intake between 800 and 1200 kcal/day depending on the composition of the conventional food eaten in the third meal [Leeds 2014]. It is provided by the European directive that, the formula diets are useful for the intended use as part of an energy-restricted diet and other food should be a necessary part of such diet [European Directive No 96/8 1996]. Main meals can be replaced flexibly by formula products, which allow an individual weight management. A meta-analysis of studies using meal replacements indicating that weight loss plans including meal replacements are more effective than conventional diets, while the energy goal for the groups was equivalent [Heymsfield et al. 2003, Busetto et al. 2011]. Meal replacements have been used in some clinical trials, such as “The Look Ahead (Action for Health in Diabetes) trial”, which examined 5145 overweight and obese adults with type 2 diabetes randomized to usual care or an intensive lifestyle intervention that included use of meal replacements. Fifty per cent of the intensive intervention participants achieved more than 5% of weight loss for 8 years [Look AHEAD Research Group 2014]. Several different studies suggest that meal replacements considerably increase the number of responder [Cheskin et al. 2008, Metzner et al. 2011] and improve weight-related risk factors such as WC, glucose- and insulin levels, lipid profile, and blood pressure when using formula diet products as partial meal replacements [Ditschuneit et al. 1999, Noakes et al. 2005, Lee et al. 2009, Flechtner-Mors et al. 2010, Smith et al. 2010, Metzner et al. 2011, Shirai et al. 2013, Khoo et al. 2014, Koohkan et al. 2014] (**Table 4**).

Total meal replacement

The use of formula products as total meal replacement is characterized by replacement of the whole daily food intake. A formula diet with a total energy intake of 800 to 1200 kcal per day results a weight reduction of 0.5 to 2 kg/week [Hauner et al. 2007]. Moreover, formula diets can use as part of a VLCD. This diet is limited to an energy intake of 800 kcal/day and should only be used for people with BMI ≥ 30 kg/m^2, who have to lose weight quickly for medical reasons (e.g., surgical intervention) [Hauner et al. 2007]. The radical break of eating habits provides a dietary change for weight reduction. These VLCDs represent a structured diet for weight management and stress of ad libitum food selection is lowered in many

subjects during the regular abstinence period [Heymsfield et al. 2003]. To ensure a safe use of VLCDs recommendations are given by the European Guideline 96/8/EC:

- the use is limited to a maximum of 12 weeks,
- VLCDs should not use for more than three weeks without medical control,
- water intake should be at least 1.5 to 2 liter per day (in addition to that mixed with the powder),
- and the use of VLCDs by adolescents, pregnant and lactating women or those with severe heart, liver or kidney diseases should be avoided.

During period of weight reduction, especially in uncontrolled applications, the risk of side effects and complications increases. The most common minor side effects occurring are flatulence, constipation, feeling cold, dizziness, fatigue and headache [Christensen et al. 2011, Leeds 2014]. Further studies have shown an elevated risk for gall stone diseases in the weight maintenance period after weight loss [Johansson et al. 2011] or electrolyte imbalance that can cause muscle and nerve malfunction [Anderson et al. 1992]. Christensen et al. (2011) compared in a randomized clinical trial a LCD (810 kcal/day) with a VLCD (420 – 554 kcal/d) for eight weeks. Both diets are followed by a fixed energy diet (1200 kcal/day) with food and two diet products daily for eight weeks. The LCD and VLCD were equally successful in inducing weight loss and decrease obesity-related symptoms. However, the VLCD results in more side effects compare to a LCD [Christensen et al. 2011]. A meta-analysis of six randomized trials demonstrated that VLCDs, compared with LCDs, lead to greater initial short-term weight loss (16.1 ± 1.6% vs. 9.7 ± 2.4% of initial body weight) [Tsai and Wadden 2006]. However, the long-term outcome seems to be no better than moderate energy-restricted diets [Abete et al. 2006, Johansson et al. 2011, Hemmingsson et al. 2012].

Formula diets with different macronutrient relations

In the context of the low carb and high protein debate, the use of formula diets for weight loss with different macronutrient relations is increasingly discussed. The compositional requirement of formula diets offers a balanced ratio of protein, carbohydrate and fat in reduced quantitates. Several studies investigated the effect of an energy-restricted diet with protein-enriched meal replacements compared with a high carbohydrate conventional diet without meal replacements for weight control. The higher protein content of a diet by protein-enriched meal replacements may produce both favorable and unfavorable metabolic effects in comparison with conventional high carbohydrate/low fat diets (Table 4). Flechtner-Mors et al. (2010) investigated the topic by randomizing 110 subjects with obesity and the MetS to either a protein-enriched diet group with meal replacements (1.34 g protein/kg body weight) or to an isocaloric conventional protein diet without meal replacements (0.8 g protein/kg body

weight). After 12-month treatment, subjects with MetS in the high protein group lost more body weight while preserving FFM compared with those on the conventional protein diet. Also parameters associated with the MetS improved in both diet groups, but improvements were only modestly greater in subjects with the high protein diet [Flechtner-Mors et al. 2010]. However, the study design did not allowed to ascribe the weight loss differences clearly to the different macronutrient compositions of the diets [Flechtner-Mors et al. 2010]. In addition, König et al. (2008) investigated the effects of a meal replacement strategy or a LCD in obese subjects. The data suggests that the meal replacement strategy is more effective in reducing metabolic risk factors and improving anthropometric measures than a LCD [König et al. 2008].

However, the current study data about formula based meal replacement strategies with different macronutrient relations for obesity treatment is insufficient. Only few studies investigated the effect of high protein meal replacement strategies compared with high carbohydrate meal replacement strategies for weight loss (Table 4). Two placebo controlled randomized trials over a period of 12 weeks demonstrated that the use of meal replacement for one or two meals with a high protein or high carbohydrate formula diet results an equal weight loss [Treyzon et al. 2008, Lee et al. 2009]. Therefore, further studies are recommended to compare the efficacy of formula diets (as total and partial) meal replacement strategies with different macronutrient composition on weight loss and metabolic derangements in obese subjects.

Table 4: Changes on weight loss as well as biochemical and metabolic parameters in some selected meal replacement studies

Reference	Study data	Diets	Weight loss and body composition	Glucose and lipid metabolism	Inflammation markers
Diets with meal replacement vs. conventional diets without meal replacement					
Kooh et al. 2013	n=46 obese men; 12 weeks; MR group: two MR/day	MR group: 36% P; 51% CHO; 17% fat pro portion Conventional diet: 20% P; 50-55% CHO; 25-30% Fat	-4.2 kg vs. -2.6 kg body weight; -4.8 cm vs. -2.5 cm WC*; -2.5 kg vs. -1.6 kg BFM; -0.5 kg vs. -0.3 kg LBM*	-0.3 mg/dl vs. -0.2 mg/dl Glucose; -5.6 mg/dl vs. -3.4 mg/dl; -1.8 vs. -1.3 HOMA-IR;	-1.2 mg/L vs. -2.2 mg/L CRP*
Koohkan et al. 2014	n=380 obese women; 12 month; MR group: two MR/day within first six weeks, and once a day in the following weeks + lifestyle program (exercise and psychology instruction)	MR group: soy based (53.3% P/meal) Conventional diet: low fat, carbohydrate consciousness and high protein diet	-7.6 kg vs. -6.6 kg body weight	Not reported	Not reported
Metzner et al. 2011	n=105 obese women; 12 weeks; MR group: replace breakfast and dinner with MR (e.g., shakes, soups or bars);	MR group: macronutrient relation not reported, 1200 kcal/day Conventional diet: 15-20% P; 50-55% CHO; 30% fat	-6.1 kg vs. -4.8 kg body weight; -6.6 cm vs. -5.3 cm WC; -4.7 kg vs. -4.1 kg BFM; -0.9 kg vs. -1.1 kg BCM; -1.3 kg vs. -0.8 kg LBM	+0.6 mg/dl vs. -2.7 mg/dl Glucose; -16.7 mg/dl vs. -11.2 mg/dl TC; -13.0 mg/dl vs. -9.1 mg/dl LDL-C; -25.3 mg/dl vs. -10.9 mg/dl TAG; -3.7 mg/dl vs. -3.5 mg/dl HDL-C	Not reported

Shirai et al. 2014	n=229 obese subjects with type 2 diabetes; 24 weeks; MR group: replace breakfast with MR (240kcal/meal) and two low caloric meals	MR group: 18% P; 52 % CHO; 30% Fat Conventional diet: 15% P; 60% CHO; 25% Fat	-3.5 kg vs. -1.4 kg body weight*	-12.1 mg/dl vs. -5.2 mg/dl Glucose; -3.6 vs. -1.3 mU/dl Insulin; -1.8 vs. -0.5 HOMA-IR; -3.2 mg/dl vs. -2.7 mg/dl LDL-C; -22.6 mg/dl vs. -1.1 mg/dl TAG*; -2.8 mg/dl vs. -0.6 mg/dl HDL-C**	Not reported
Very low calorie diets vs. low calorie diets					
Christensen et al. 2011	n=192 obese subjects; 16 weeks; **1.** Phase of the study (8 weeks) VLCD: three – four portion of formula diets dissolved in water/day LCD: four portions of formula diets dissolved in skimmed milk and water/day **2.** Phase of the study (8 weeks) both groups replace two meals/day	**1**. VLCD: 41% P; 41% CHO; 18% fat (415 kcal/day) LCD: 41% P; 46% CHO; 13% fat (810 kcal/day) **2**. 1200 kcal/day	**1.** -11.4 kg vs. -10.7 kg body weight; -8.6 cm vs. -8.1 cm WC **2.** -13.3 kg vs. -12.2 kg body weight; -10.6 cm vs. -9.9 cm WC	**1.** -6.0 mg/dl vs. -7.7 mg/dl Glucose; -28.2 mg/dl vs. -32.5 mg/dl TC; -18.9 mg/dl vs. -19.7 mg/dl LDL-C; -5.3 mg/dl vs. -11.5 mg/dl TAG; -5.8 mg/dl vs. -7.1 mg/dl HDL-C **2.** -5.0 mg/dl vs. -6.3 mg/dl Glucose; -13.1 mg/dl vs. -15.1 mg/dl TC; -7.7 mg/dl vs. -8.5 mg/dl LDL-C; -7.1 mg/dl vs. -6.2 mg/dl TAG; -1.5 mg/dl vs. -2.7 mg/dl HDL-C	**1.** -0.3 mg/L vs. -0.6 mg/L **2.** -0.5 mg/L vs. -0.5 mg/L CRP

Hemmingsson et al. 2012	n=9037 obese subjects; one year; VLCD: total MR with formula diets for 6-10 weeks followed by gradual intake of normal food LCD: two MR/day and two energy-restricted meals	VLCD: 500 kcal/day LCD: 1200 – 1500 kcal/day	-11.5 kg vs. -6.8 kg body weight*; -8.6 cm vs. -5.9 cm WC*	Not reported	Not reported
High protein formula diets vs. conventional high carbohydrate diets					
Flechtner-Mors et al. 2010	n=110 obese subjects with; MetS; 12 month; High protein group: two protein-enriched MR, one normal meal and two snacks for the first three month vs. conventional diet: three meals and two snacks without MR for the first three month	High protein: 30% P; 40% CHO; 30% fat Conventional diet: 15% P; 55% CHO; 30% fat	-9.1 kg vs. -6.4 kg body weight*; -12.1 cm vs. -8.2 cm WC*	-10.0 mg/dl vs. -11.0 mg/dl Glucose; -10.6 vs. -17.8 mU/dl Insulin; - 5.1 mg/dl vs. -4.6 mg/dl TC; -62.0 mg/dl vs. -10.7 mg/dl TAG*; +2.5 mg/dl vs. -0.04 mg/dl HDL-C	-1.5 mg/L vs. 0.12 mg/L CRP*
König et al. 2008	n=90 healthy obese subjects; six weeks; High protein group: two high soy-protein MR + lifestyle education (include	High protein: macronutrient relation not reported, 1000-1200 kcal/day Conventional diet: 15% P; 60% CHO; 25% fat (1200-	-6.4 kg vs. -3.0 kg body weight**; -6.1 cm vs. -1-7 cm WC**; -5.1 kg vs. -2.8 kg BFM	-4.0 mg/dl vs. -3.8 mg/dl Glucose; -5.1 vs. -0.58 mU/dl Insulin; -29.0 mg/dl vs. -16.0 mg/dl TC; -16.0 mg/dl vs. -9.0 mg/dl LDL-C; -19.0 mg/dl vs. +12.0 mg/dl TAG; -7.5 mg/dl vs. -7.0 mg/dl HDL-C	Not reported

	physical activity) vs. conventional diet: received the same lifestyle educations	1800 kcal/day)			
High protein formula diets vs. high carbohydrate formula diets					
Lee et al. 2009	n=75 obese subjects with MetS; 12 weeks; Two MR and one normal meal/day	High protein: 30% P; 50% CHO; 20% fat High carbohydrate: 15% P; 65%CHO; 20% fat and 25 g fiber	-5.0 kg vs. -4.9kg body weight; -6.3 cm vs. -7.1 cm WC; -2.5 kg vs. -2.3 kg BFM	-3.8 mg/dl vs. -4.2 mg/dl Glucose; -7.4 vs. -8.9 mU/dl Insulin; -18.6 mg/dl vs. -11.1 mg/dl TC; -70 mg/dl vs. -56.4 mg/dl TAG; +5.9 mg/dl vs. +7.6 mg/dl HDL-C	Not reported
Treyzon et al. 2008	n=100 healthy obese subjects; 12 weeks; Two MR and two normal meals/day	High protein: 30% P; 40% CHO; 30% fat High carbohydrate: 15% P; 55% CHO; 30% fat	-4.2 kg vs. -3.7 kg body weight; -6.7 cm vs. -5.1 cm WC; -1.6 kg vs. -0.6 kg BFM; -2.7 kg vs. -4,1 kg FFM	-3.9 mg/dl vs. -0.7 mg/dl Glucose; -13.1 mg/dl vs. -8.5 mg/dl TC; -8.4 mg/dl vs. -10.6 mg/dl LDL-C; -14.7 mg/dl vs. -3.2 mg/dl TAG; +0.6 mg/dl vs. +2.7 mg/dl HDL-C	Not reported

Data are shown as mean ± standard deviation; BCM: body cell mass; BFM; body fat mass; CHO: carbohydrate; HDL-C: high-density lipoprotein; CRP: C-reactive protein; HOMA-IR: homeostasis model assessment for insulin resistance; LDL-C: low-density lipoprotein cholesterol; MR: meal replacement; TAG: triacylglycerol; TC: total cholesterol; WC: waist circumference; Difference between the groups was significant at *$p<0.05$; **$p<0.001$.

1.3 Objectives

The loss of weight and improved obesity-related derangement can be achieved by reducing energy uptake either through formula diets, energy-restricted diets with changed macronutrient relation or diets with low GI. However, selecting low-calorie foods with prescribed macronutrient composition to provide beneficial high carbohydrate, high protein or low-GI diets are associated with poor adherence and may be difficult to maintain by conventional dietary approaches. In the context of the current discussion of „low carb“ vs. „low fat“ diets there is much debate about different relations of macronutrient content in formula diets used as meal replacements.

However, the effect of formula based meal replacement strategies with varying macronutrient composition for obesity treatment is insufficient. Limited data are available about the GI of protein- and carbohydrate-enriched formula diets with regard to weight loss. In addition, barely information exists about inflammation markers and oxidized hydroxy, epoxy and dihydroxy PUFA levels in pathophysiological states like obesity as well as the effect of diet-induced weight loss on inflammation state and oxylipin patterns. Whether different macronutrient compositions of formula diets are used as partial or total meal replacement may be the perfect option to effects weight loss and metabolic derangements (e.g., hyperglycemia, dyslipidemia, hypertension, or inflammation state) in obese and overweight people have to clarify.

Thus, this thesis investigated the efficacy of two isoenergetic formula diets with different focus on proteins, carbohydrates and fats. This was specifically aimed to determine:

1. How effects total and partial meal replacement strategies with formula diets either high in carbohydrates or high in proteins weight loss in overweight and obese subjects? (**Paper I**)

2. What are the differences of a high carbohydrate and a high protein formula diet used as partial meal replacement on body composition and metabolic risk parameters in overweight and obese subjects? (**Paper II**)

3. How are the concentrations of inflammation markers and oxylipin levels in obese subjects with no and low grade inflammation and to what extent are they affected by a formula based low calorie diet? (**Paper III**)

4. How formula diets either high in carbohydrate or high in protein does affect the postprandial glucose and insulin secretion to determine the glycemic index? (**Paper IV**)

2. Paper I: Efficacy of high carbohydrate versus high protein meal replacements on weight reduction – A randomized controlled trial

Efficacy of high carbohydrate versus high protein meal replacements on weight reduction - a randomized controlled trial. Möller K, Willers J, Hahn A. *J Obes Weight Loss Ther* 2015; 5 (3): 1-9.

http://www.omicsgroup.org/journals/efficacy-of-high-carbohydrate-versus-high-protein-meal-replacements-onweight-reduction--a-randomized-controlled-trial-2165-7904-1000266.php?aid=54708

ABSTRACT

Background: While formula diets as meal replacements are evident for weight loss, the macronutrient composition is still in the focus of interest. This study was designed to determine effects of a carbohydrate-riched meal replacement on weight loss and waist circumferences (WC) in comparison with a protein-riched meal replacement.

Methods: Two groups (high carbohydrate formula diet (HC) and high protein formula diet (HP)) of 80 matched subjects each underwent a randomized parallel intervention trial for eight weeks followed by a 12-week follow-up. The intervention consisted of three phases: (1) week 1 and 2: total replacement of three meals, (2) week 3 and 4: replacement of two meals and (3) week 5 to 8: replacement of one meal. Measurements were taken at week 0, 2, 8, and 20.

Results: After two weeks of total meal replacement, there was a significant ($p < 0.001$) weight loss in both groups (HC: -4.0 ± 4.7 kg vs. HP: -4.3 ± 1.8 kg). After eight weeks, 66.2% of all subjects achieved a weight loss of 5% and more (HC: -8.5 ± 2.5%, $p < 0.001$ vs. HP: -8.8 ± 2.8%, $p < 0.001$), and 18.2% of the participants lost more than 10% of their initial body weight. Waist circumferences decreased from 105.9 ± 9.7 cm to 97.4 ± 8.4 cm ($p < 0.001$) after eight weeks. During the follow up, further weight loss was observed in both groups. There were no significant differences between the HC and HP-group regarding changes in weight and WC.

Conclusion: Both dietary intervention strategies had a similar effect on weight loss and WC reduction. In this short-term study macronutrient compositions of meal replacements are not crucial for the efficacy of formula diets.

Trial registration: German Clinical Trials Register DRKS00005481

Key words: meal replacement; formula diet; weight loss; high carbohydrate; high protein

3. Paper II: Effects of a high carbohydrate and high protein formula diet on body composition and metabolic risk parameters in overweight and obese subjects

II

Effects of a high carbohydrate and high protein formula diet on body composition and metabolic risk parameters in obese subjects. Möller K, Schneider I, Willers J, Hahn A. *J bes Weight loss Ther* 2015; 5 (6):1-7.

http://www.omicsgroup.org/journals/effects-of-a-high-carbohydrate-and-high-protein-formula-diet-on-bodycomposition-and-metabolic-risk-parameters-in-obese-subjects-2165-7904-1000291.pdf

ABSTRACT

Background: In obese subject's weight loss is known to improve blood lipid profiles, glycemic control and other conditions that may contribute to the development of metabolic syndrome or cardiovascular diseases. However, the optimal dietary carbohydrate and protein composition to facilitate weight loss and improving potential adverse effects is still in debate. Therefore, the aim of this study was to compare the effect of two low-fat formula diets either high in carbohydrate or high in protein, on body composition and metabolic risk factors.

Methods: 154 obese (BMI 32.5 ± 0.14 kg/m^2) men and women were included in this randomized clinical trial and classified in two groups (high carbohydrate formula diet (HC) and high protein formula diet (HP)) of 80 matched subjects. They underwent an intervention for eight weeks, which consisted of two phases: (1) week 1 and 2: total replacement of three meals by a formula diet and (2) six week partial formula diet (replacement of 1-2 meals). Measurements were taken prior and post intervention for analysis of body composition and parameters of lipid and glucose metabolism.

Results: After eight weeks both groups lost significantly body fat mass (HC: -5.11±0.51 kg, $p<0.001$; HP: -5.81±0.54 kg, $p<0.001$), while only for subjects of HP group no change of lean body mass and body cell mass was observed. Metabolic risk parameters were reduced in both the HC and HP group; however, subjects in the HC group showed a higher reduction in triacylglycerol concentration (-29.1 mg/dl vs. -14.0 mg/dl, $p<0.04$). Further, the prevalence of the metabolic syndrome was reduced in both groups without difference (HC: -17.9%, $p=0.004$; HP: -18.4%, $p=0.003$).

Conclusion: Our data demonstrate, that even in a short period of time, a low-fat meal replacement diet high in carbohydrate or high in protein is effective in improving body composition and reducing metabolic risk parameters.

Key words: Carbohydrate; Protein; Formula diet; Obesity; Body composition; Metabolic risk parameters

4. Paper III: Influence of weight reduction on blood levels of C-reactive protein, tumor necrosis factor-α, interleukin-6, and oxylipins in obese subjects

III

Influence of weight reduction on blood levels of C-reactive protein, tumor necrosis factor-α, interleukin-6, and oxylipins in obese subjects. Möller K, Ostermann AI, Rund K, Thoms S, Blume C, Stahl C, Hahn A, Schebb NH, Schuchardt JP. *PLEFA* 2016; 106: 39-49.

http://www.sciencedirect.com/science/article/pii/S0952327815300454

ABSTRACT

Introduction: Obesity is associated with inflammation and weight reduction has been shown to influence the inflammatory process. Besides classic inflammatory markers, oxidized polyunsaturated fatty acid (PUFA) metabolites (oxylipins) are potent mediators of inflammation. Little is known about endogenous levels of oxylipins, e.g. hydroxy, epoxy and dihydroxy FA in obese subjects with persistent low-grade inflammation. We aimed to evaluate levels of inflammatory markers and blood oxylipins in obese subjects before and after weight reduction.

Subjects and methods: In the present study, 42 obese (BMI 32.7 ± 0.22 kg/m^2) men and women were classified in groups according to high-sensitivity C-reactive protein (hsCRP) levels (no inflammation < 1 mg/L; low-grade inflammation ≥ 3 mg/L). Subjects underwent an intervention for eight weeks, which consisted of two phases: (1) week 1 and 2: total replacement of three meals by a formula diet and (2) six week partial formula diet (replacement of 1-2 meals). Blood samples were taken prior and post intervention for analysis of plasma protein levels of hsCRP, tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6). Plasma Levels of free (unesterified) hydroxy, epoxy, and dihydroxy FAs as well as several prostanoids were analyzed in plasma by means of LC-MS-based targeted metabolomics.

Results: At baseline subjects with low-grade inflammation (hsCRP 8.95 ± 1.39 mg/L) showed significant higher levels of IL-6 (22.7 ± 1.15 ng/L) and TNF-α (17.4 ± 0.75 ng/L) compared to subjects with no inflammation (hsCRP: 0.69 ± 0.05 mg/L; IL-6: 15.9 ± 1.18 ng/L; TNF-α: 14.6 ± 0.80 ng/L). In both group's body weight was significantly reduced ($p<0.001$) after intervention (no inflammation group: -7.19 ± 0.86 kg, -7.3 ± 0.89%, $p<0.001$; low-grade inflammation group: -6.78 ± 0.87 kg, -6.7 ± 0.81%, $p<0.001$). Moreover, we observed significant decreases in levels of hsCRP (4.66 ± 0.64 mg/L; $p=0.006$), IL-6 (6.81 ± 1.15 ng/L; $p<0.001$) and TNF-α (6.09 ± 0.47 ng/L; $p<0.001$) in subjects with low-grade inflammation. Of 60 quantified oxylipins, 11 linoleic acid (LA)-, 1 dihomo-γ-linolenic acid (DGLA)-, 7 alpha linolenic acid (ALA)-, 15 arachidonic acid (AA)-, 8 eicosapentaenoic acid (EPA)- and 18 docosahexaenoic acid (DHA)-metabolites could be detected in plasma. For most oxylipins no differences were found between the low and high hsCRP groups before and after weight reduction. Interestingly, in subjects with low- grade inflammation several AA-derived oxylipins

(5-, 8-, 12-hydroxyeicosatetraenoic acids (HETE)) were significantly higher compared to subjects with no inflammation before weight reduction and significantly reduced after weight reduction.

Conclusion: Even moderate weight loss in obese subjects correlates to a significant improvement in the inflammatory state, by reducing hsCRP, IL-6, TNF-α and few oxylipins. The biological consequences of these changes remain to be further investigated.

Key words: Inflammation, Obesity, Weight Loss, Oxylipins, PUFA

5. Paper IV: Glycemic index and glycemic load of a carbohydrate-rich and protein-rich formula diet

IV

Glycemic index and glycemic load of a carbohydrate-rich and protein-rich formula diet. Möller K, Willers J, Schneider I, Hahn A. *J Nutr Health Sci* 2015; 2 (4): 406

https://nutritionandhealthsciences.wordpress.com/2015/11/21/glycemic-index-and-glycemic-load-of-a-carbohydrate-rich-and-protein-rich-formula-diet/

ABSTRACT

Obesity is well associated in various chronic diseases such as type 2 diabetes, hyperinsulinemia, dyslipidemia and atherosclerosis. Thus, for persons with obesity and diabetes, food with low GI are recommended in order to lower the glycemic response. The aim of this study was to examine the glycemic index (GI) and glycemic load (GL) of two formula diets, which are carbohydrate-rich (HC) or protein-rich (HP). Twenty healthy volunteers aged 25.8 ± 5.8 years (body mass index: weight/height^2 = 23.8 ± 2.4 kg/m^2) randomly received either a reference food or amounts of the test food with equal carbohydrate content (45.9 g glucose / portion) in three visits with at least 6 days between each intervention; resulted in a portion size of 76.2 g HC and 147.1 g HP. In order to determine plasma glucose and insulin concentrations, seven blood samples were collected (basal, 15, 30, 45, 60, 90 and 120 min after intake of the test foods). Satiety was reported on a visual analog scale during the test phase of two hours. In relation to glucose, a GI of 66.9 ± 41.8 was measured for HC formula diet and 7.1 ± 7.2 for HP formula diet. The GL of the HC serving portion was found to be 22.8 ± 14.3 and for HP 1.8 ± 1.9. This result indicates that HC can be classified as a medium GI food (55 - 69) and HP as low GI food (< 55). In addition, self-reported hunger and satiety levels were more pronounced with HP compared to glucose ($p < 0.05$). The GI and GL of the HP formula diet seemed to be more favorable and achieved good effects in view of a low glycemic response.

Key words: glycemic index, glycemic load, formula diet, high carbohydrate, high protein, cross-over study

6. General Discussion

The main purpose of these studies presented in this thesis was to investigate the impact of formula diets uses as total and partial meal replacements with varying macronutrient composition on weight loss, body composition and metabolic parameters of the carbohydrate and fat metabolism on obese and overweight individuals. In this context, the influence of a formula based low-calorie diet was analyzed to clarify the effects on inflammation markers and plasma oxylipins levels in obese subjects with no and low-grade inflammation. For these purposes, a randomized, monocentric human intervention study of eight weeks including a follow-up of 12-weeks were undertaken with overweight and obese men and women. The subjects of the trial consumed either a high carbohydrate formula diet or a high protein formula diet. The results of this interventional study are demonstrated into three parts with different main focuses, which are presented within this thesis in **Paper I, II** and **III**.

Additionally, this thesis considers the influence of both formula diets on postprandial glucose and insulin metabolism to measure the GI. This term is useful for quantitative assessment of these formula diets as foods for obesity treatment. Furthermore, self-reported postprandial satiety has been measured. To determine the glycemic response and satiety of both formula diets, a randomized, monocentric crossover trial in healthy, non-smoking, non-diabetic men and women were conducted. The main results of this trial are shown in **Paper IV**.

In this section, the results of both intervention trials are discussed in the context of formula diets with different macronutrient relation and glycemic response on body weight, body composition and metabolic risk factors.

6.1 Formula diets with different macronutrient composition on weight loss

Paper I demonstrates how formula based low dietary fat intake with either a high carbohydrate or a high protein intake modulates weight loss and WC in obese and overweight subjects. To take account of a total meal replacement plan on weight loss, we selected three formula diets per day in the first two weeks. This total meal replacement achieved weight loss rates about 2 kg per week, which is in accordance with studies used LCD (800 – 1000 kcal/day) for weight loss [Hauner et al. 2007, Due et al. 2008, Christensen et al. 2011]. In the period between week five and week eight of intervention, subjects had to replace one - two meals per day by formula diets and eat conventional meals prepared according to the principles of a balanced diet. Within the last six weeks of partial meal replacement additional weight loss of 2.5 ± 2.6 kg was observed. Thus, both diet groups achieved an overall weight loss of 6.7 ± 3.6 kg. The more pronounced weight loss effects

during the total meal replacement compared with the partial meal replacement was expected. This variation of weight loss can partly be explained by different energy intake during total meal replacement (approx. 900 kcal/day and partial meal replacement (approx. 1400 kcal/day). This is in accordance with Hemmingsson et al. (2012), who demonstrated that subjects prescribed a total meal replacement with formula diets (approx. 500 kcal/day) achieved significantly more weight loss compared to subjects of a partial meal replacement group (approx. 1200–1500 kcal) [Hemmingsson et al. 2012].

The total meal replacement of the first two weeks enabled a controlled macronutrient intake of both dietary groups. To estimate the full potential of a formula based high carbohydrate diet in comparison to a high protein diet on weight loss it is required a longer period. However, long-term total meal replacement interventions might increase drop-out rates and have to carry out under medical control. Despite the fact that the intake of energy-restricted meals was not controlled during partial meal replacement, the difference between carbohydrate and protein intake in both groups was still maintained. This offers a further estimation of formula based high carbohydrate and high protein meal plan. Although self-reported food diaries may not provide accurate information, the delivered data could be used to assess macronutrient intake.

Selecting the optimal composition of macronutrients for a low-calorie meal plan is an important consideration for the initiation and maintenance of weight loss for overweight and obese patients. Study results often mentioned that substitution of carbohydrates or proteins for fat may be the main reason for weight loss and weight maintenance [Champagne et al. 2011]. Additionally, weight loss is improved by adherence to a reduced fat intake [Swinburn et al. 2001]. Therefore, low fat formula diets are useful to facilitate the completion of recommended diet plans to improve weight loss. In contrast to study results, which obtained increased weight loss by high protein and low fat intake compared to a high carbohydrate low fat diet plan [Noakes et al. 2005, Meckling and Sherfey 2007, Clifton et al. 2009], these results demonstrated that both dietary patterns were equally successful in inducing weight loss, independently of diet composition. A modest weight loss up to 5% of initial body weight was resulted in 65.4% of the high carbohydrate group and 67.1% of the high protein group. While other studies achieved no protection against weight regain through high protein or high carbohydrate intake [Lejeune et al. 2005, Delbridge et al. 2009, Dale et al. 2009]. This study observed weight maintenance of initial weight loss and no weight regain in both formula diet groups after 20 weeks ($p<0.001$, respectively). Subjects in the high carbohydrate formula diet group, who lost over 5% of initial body weight in the first two weeks, gained weight after 12 weeks of follow up (0.34 kg; 0,26 %). However, this weight gain was not significantly different to the high protein formula diet group.

One argument against the use of formula diets is the higher sugar content. Sugar is often used to make formula diets tastier but it is also assumed to be important for increasing energy intake and obesity development [Malik et al. 2012, Bray and Popkin 2014]. The sugar content of the formula diets was 48.9% of total calories per portion for high carbohydrate and 34.3% of total calories per portion for high protein formula diet. The WHO guideline recommends reducing daily intake of free sugars (such as glucose and fructose) to less than 10% of total energy intake [WHO 2015a]. Whereby, the guideline does not refer to sugars naturally contained in milk. In the used formula diets, the sugar content mainly comes from the mixed milk for preparation. Various clinical trials demonstrate that sugar containing formula diets as meal replacements can lead to a significant weight loss [Heymsfield et al. 2003, Drewnowski and Bellisle 2007, Bischoff et al. 2011].

Next to described macronutrient content of the meal plans, the energy intake was observed. The advice to reduce dietary energy intake is currently referred as a strong recommendation for weight loss strategies [Sacks et al. 2009, Abete et al. 2010]. In this study, food records had shown a significant reduction of energy intake during the first two weeks of intervention (high carbohydrate group 65.2% and high protein group 60.1%, $p<0.001$ respectively). The next six weeks of intervention and 12 weeks of follow up with self-conducted partial meal replacement caused a continual increase of energy intake, which was still reduced in both groups compared to baseline ($p<0.001$, respectively). Therefore, the decreasing effect of body weight demonstrated for both formula diets might be attributed to a reduced energy intake during the formula based meal replacement intervention. Additionally, the energy restriction provides an effective option for maintenance of initial weight loss and reduced weight regain. Due to poor compliance and high dropout rates, this effect was less consistent in energy-restricted conventional diet trials [Brinkworth et al. 2004, Dansinger et al. 2005]. Therefore, the use of high carbohydrate or high protein formula diets may effective to create a bigger energy deficit and realize beneficially higher carbohydrate or protein dietary approaches than maintaining usually with a conventional diet.

6.2 Formula diets with different macronutrient content on body composition

Paper II demonstrated how formula based energy restriction and different macronutrient relations modulate changes of body composition.

Weight loss induced by energy-restricted diets has often been associated with loss of BFM in addition to reduction of LBM [Layman et al. 2003, Layman et al. 2009]. LBM is essential for weight maintaining after weight loss because it leads to retention of resting energy expenditure [Vogels et al. 2005]. The results demonstrated that both low fat diets lead to comparable reductions of BFM, while only subjects with higher protein intake showed

retention of LBM and BCM. Several studies observed similar results, which suggested that high protein intake has been associated with no change of LBM compared to high carbohydrate intake [Farnsworth et al. 2003, Krieger et al. 2006, Leidy et al. 2007]. In this study the daily protein intake of the high protein meal replacement plan was close to the suggested cut off level >1.05 g protein/kg body weight. Additionally, the EFSA suggested a daily protein intake during low calorie diets of 75 g/day to avoid LBM loss [EFSA 2015a]. The formula based high protein diet exceeded the dietary intake of 75 g protein in both dietary meal replacement plans (total and partial). By contrast, intakes of formula diet with high carbohydrate content did not achieve the recommended protein amount. Therefore, these results provide the effect, that dietary protein might be dependent to maintain LBM and BCM. The physical activity has been monitored during the study, but the actual influence cannot be quantified.

6.3 Formula diets with different macronutrient composition on obesity-related metabolic disorders

As a consequence of the formula based low calorie diets, both meal plans resulted in improvements of metabolic and cardiovascular risk parameters, which was demonstrated in Paper II and III.

Both low fat formula diets were similar in their effects on induced change of dyslipidemia (Paper II). Reduced TC, LDL-C and TAG levels can be observed in many other formula based weight loss studies too, as well as the initial decrease in HDL-C [König et al. 2008, Treyzon et al. 2008, Lee et al. 2009, Metzner et al. 2011]. After 12 weeks of follow-up blood lipid levels were still significantly lower than at baseline. In general, these changes might be attributed to weight loss diets with lower fat content. Unlike other weight loss studies [Layman et al. 2003, Noakes et al. 2005, Dansinger et al. 2005, König et al. 2008], the difference of TAG levels reflected a significantly higher reduction by high carbohydrate formula diet. Usually, the assumed mechanism is that higher carbohydrate intake might lead to a higher synthesis of hepatic VLDL particles and a potentially increased TAG production [Clifton et al. 2009]. Furthermore, it is suggested that sparing amounts of carbohydrates attenuating postprandial insulin secretion, which increases fat oxidation [Brinkworth et al. 2004]. However, prescribed diets contained a carbohydrate intake about 55-60% of total energy [Noakes et al. 2005, Dansinger et al. 2005, Gardner et al. 2007, König et al. 2008, Claessens et al. 2009], whereas the formula based high carbohydrate group achieved an intake at least 50% of total energy. Thus, the self-conducted consumed meals during meal replacement may result in an underestimation effect of the formula based high carbohydrate diet.

Furthermore, both formula diets had useful effects on abdominal fat reduction measured as WC (Paper I). The reduction is of major clinical interest, because even a reduction of three cm results in a significant improvement of cardiovascular risk [Balkau et al. 2007]. The visceral adipose tissue is associated with insulin resistance and the development of low-grade inflammation [van Gaal et al. 2006]. However, both risk factors were reduced by formula based weight loss (Paper II). The used homeostasis model assessment of insulin resistance (HOMA-IR), decreased significantly ≤ 2 in both groups, which implies an improved pathological prediabetic state [Sink 2007]. Additionally, hsCRP levels improved in both formula diet groups by amounts that have significant clinical benefits on inflammation state (Paper II). Furthermore, we observed reductions of the inflammation markers TNF-α and IL-6 by the low calorie diet in subjects with no and low-grade inflammation (Paper III). These results are in accordance with diet-induced weight loss studies of obese subjects. They demonstrated reduced serum TNF-α and IL-6 levels, which are associated with improved insulin sensitivity and lipid metabolism [Roytblat et al. 2000, Bastard 2000, Esposito et al. 2003]. Therefore, this short term energy-restricted low fat diet has beneficial effects on inflammatory state in overweight and obese subjects, which are suggested to predict the progression of CVD [Ridker 2007, Eldrup et al. 2012].

These metabolic derangements are primary factors in the development of the MetS [Mottillo et al. 2010, Després 2012]. At the beginning of the study, 46.2% of the high carbohydrate group and 52.6% of the high protein group met at least three of five criteria of the Mets. The number of subjects with at least three criteria declined during the study in both formula diet groups. The influence of macronutrients on MetS prevalence remained unclear. Some studies found no effect of different macronutrient relation on MetS prevalence [Rajaie et al. 2014, Papadaki et al. 2014], while other suggested a significant decrease by energy-restricted high protein or high carbohydrate diet [McKeown et al. 2004, Flechtner-Mors et al. 2010]. Therefore, it has to be assumed, that the improvement of the various parameters of the MetS contributed differently to this outcome.

Next to the classic metabolic risk and inflammation markers we detected levels of plasma oxylipins in obese subjects without or with low-grade inflammation. It is well known, that EPA- and AA-derived epoxy FA have anti-arrhythmic, vasodilatory or anti-inflammatory effects [Westphal et al. 2011, Agbor et al. 2012, Jung et al. 2012] as well as the commonly used LOX pathway markers 5-, 12-, 15-HETE for information about inflammatory state. Furthermore, it is important to obtain information about the concentrations of PUFA derived hydroxy, epoxy and dihydroxy FA in human blood and changes in different physiological and pathophysiological states. In accordance with other studies [Lieb et al. 2014, Pickens et al. 2015] we observed increased levels of AA-derived LOX metabolites 5-HETE and 12-HETE in

obese subjects with low-grade inflammation. Whereas the majority of previous studies demonstrated changes in oxylipin patterns after long-chain omega-3 PUFA intake [Schebb et al. 2011, Schuchardt et al. 2014, Newman et al. 2014] we observed significant reductions of AA-derived metabolites (5- and 12-HETE) in the low-grade inflammation group as well as in the no inflammation group by low fat low calorie diet. It cannot be clarified, if these changes in the oxylipin pattern are a direct result of changes in the qualitative and quantitative PUFA intake. However, this result suggests that the oxylipin pattern in obese subjects can be affected by a low fat low calorie diet. Therefore, the plasma lipid profile, which is characteristic of dietary FA intake and changes in fatty acid metabolism, may contain potential biomarkers of the chronic inflammation associated with obesity.

6.4 Glycemic response and satiation effect of formula diets with different macronutrient composition relate to weight loss

In Paper IV, the glycemic response after intake of both formula diets and glucose as a reference was measured with respect to obtain the GI and GL in healthy subjects. Both, the GI and GL rank carbohydrate containing foods on the basis of their postprandial glycemic increasing effect and have received attention. The quantitative and qualitative aspects of carbohydrates may have an impact on the management of obesity and obesity-related conditions. The high protein formula diet can be classified as low GI and low GL food, whereas the high carbohydrate formula diet has to be classified as medium GI and high GL food. Low GI diets enhance weight control by contributing satiety, which induce energy restriction [McMillan-Price and Brand-Miller 2006, Thomas et al. 2007]. In a large European study, overweight adults followed a high- or low protein diet paired with either a high or low GI diet for 26 weeks. Participants consuming the low GI high protein diet achieved more weight loss and gained less weight than those following the high GI diet [Larsen et al. 2010]. By contrast, we demonstrated no difference after consumption of the low GI formula diet and moderate glycemic formula diet on weight loss and energy intake (Paper I).

In addition to GI, the satiation effect can lead to spontaneous reduction of energy intake, which importantly affects the maintaining and efficacy of weight loss strategies [Bellissimo and Akhavan 2015]. Especially dietary macronutrients make a decisive contribution to the feeling of satiety. Satiety can be evaluated by visual analog scale (VAS), which describes perceived sensations. The VAS consists of four questions on hunger, fullness, desire to eat, and prospective food consumption and is associated with hormonal response and predicts both eating initiation and subsequent meal size. The satiating effects of macronutrients indicate that protein being the most satiating followed by carbohydrates and fat [Hall et al. 2012]. In particular the content of soy protein and whey protein in the high protein formula

diet might promote satiety [Veldhorst et al. 2009]. Diets high in protein are associated with increasing satiety and decreasing energy intake, which achieve weight loss [Weigle et al. 2005]. By contrast, the high carbohydrate formula diet contains higher amounts isomaltulose, which decrease postprandial rise in plasma glucose and insulin levels [van Can et al. 2009, Holub et al. 2010]. Based on the nutritional ingredients of formula diets, both potentially influence the glycemic response and have satiating effects, which may reduce energy intake and contribute to weight reduction. However, we demonstrated higher satiating effect by higher protein content, mainly as soy protein isolate and whey protein isolate in the formula diet, compared to the high carbohydrate formula diet (Paper IV). Next to similar weight loss the food records of both formula diet groups indicate the same lowering energy intake throughout the partial meal replacement (Paper I). Thus, it may assume that high satiating effects of the high protein formula diet neither contributed to energy intake nor weight loss.

7. General Conclusion

The results from studies conducted are presented in Paper I-IV. Both formula based low calorie diets with different macronutrient composition contribute weight loss and affect obesity-related metabolic disturbances, including visceral adipose tissue, dyslipidemia, insulin resistance, inflammation and MetS. **Figure 4** gives an overview about the results.

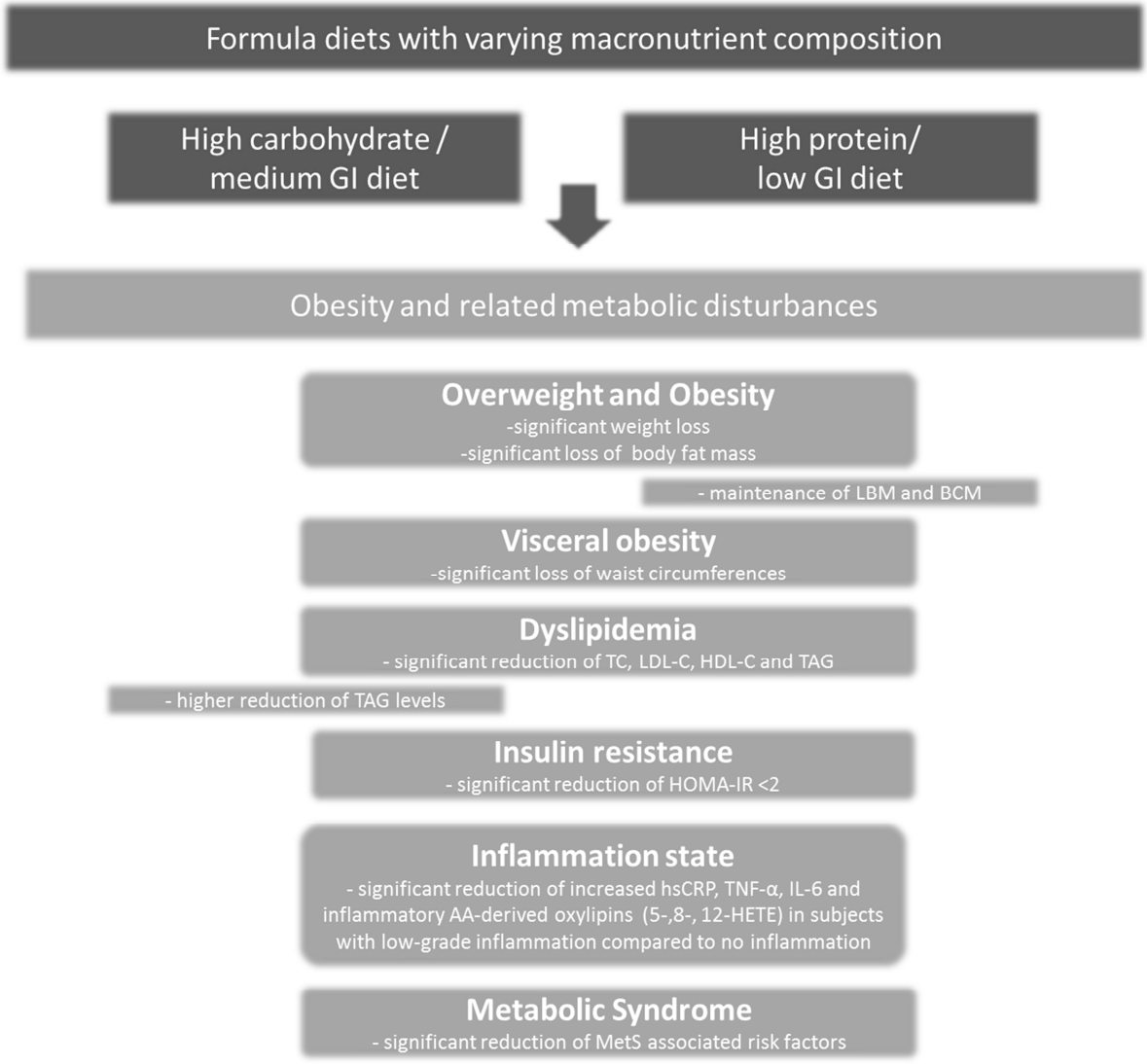

Figure 4: Obesity-related disturbances influenced by formula diets with different macronutrient composition and glycemic index

The figure summarizes the obesity-related disturbances (grey boxes) influenced by formula based changed macronutrient composition and glycemic index (blue boxes) demonstrated in Paper I-IV. BCM: body cell mass; HDL-C: high-density lipoprotein-cholesterol; HETE: hydroxyeicosatetraenoic acid; HOMA-IR: homeostasis model assessment for insulin resistance; CRP: C-reactive protein; IL-6: interleukin-6; LBM: lean body mass; LDL-C: low-density lipoprotein-cholesterol; TAG: triacylglycerol; TC: total cholesterol; TNF-α: tumor necrosis factor alpha

It can be concluded that macronutrient compositions neither of total meal replacement plans nor of partial meal replacement plans are less crucial for the efficacy of formula diets on weight loss. Additionally, both formula diets may have advantages for the management of dyslipidemia, insulin resistance, inflammation and MetS. However, possible protein and carbohydrate related crucial effects on body composition and TAG levels are presented.

Nevertheless, weight loss and improvements of obesity-related derangements of both groups may attribute to the lower energy intake of the diet, which contributes the use of formula diets. The adherence of restricting total energy intake is a major factor for achieving weight loss. Therefore, the use of high carbohydrate or high protein formula diets as meal replacement appears to be a possible opportunity to facilitate these effective dietary approaches and both could be recommended to obese persons with abnormal metabolic risk factors for the purpose of weight loss. With regard to compliance dietary strategies, the focus should be on finding an individualized dietary approach. Individuals who prefer favorable protein for weight reduction, a high protein meal replacement plan offers an opportunity. Whereby, meal replacements with high carbohydrate content provide an alternative for those who choose not to increase protein intake.

Future studies may be more successful if they include strict-controlled meals during the partial meal replacement plan to ensure prescribed carbohydrate and protein intake. Additionally, studies may be desirable to combine the high protein meal replacement strategies with resistance exercise to demonstrate significant differences in the retention of LBM and BCM during weight loss. Investigations have to clarify the physiologic systems that govern food intake and energy balance to fully realize the advantages of macronutrient composition in weight loss. This study represent only a short-term effect over eight weeks, which could lead to an underestimation of the full potential of the formula based high carbohydrate or high protein meal replacements. Studies demonstrating long-term effects with regard to lasting weight management are required.

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07/2010	Bachelor of Science
10/2010-06/2013	Studium an Universität Wien Fachrichtung: Molekulare Ernährung
06/2013	Master of Science
seit 10/2013	Studium an Leibniz Universität Hannover Promotion Lebensmittelwissenschaft

Praktika

07/2008 - 10/2008	Institut für Ernährungspsychologie und Optifast Ambulanz, Göttingen
05/2009	Mitwirkung Jahresstudie „Nutrition Day“ Klinikum Wien, Arbeitsgemeinschaft für klinische Ernährung, Wien
12/2010 – 01/2011	Mitwirkung Projekt im Bereich der Lebensmittelwerbung, Fakultät für Lebenswissenschaft – Emerging Focus Nutrigenomics, Wien
08/2011	Mitarbeit Österreichischen Ernährungsbericht 2012, Wien

Berufserfahrung

seit 04/2012	Wissenschaftliche Hilfsmitarbeiterin am Institut für Lebensmittelwissenschaft und Humanernährung, Leibniz Universität Hannover

Besondere Kenntnisse

Fremdsprachen	Englisch sehr gute Kenntnisse Spanisch gute Kenntnisse
PC-Kenntnisse	gängige Office-Anwendungen Umgang mit Internet und E-Mail Statistikprogramm SPSS