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# Diet, Lifestyle and Chronic Complications in Type 1 Diabetic Patients

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## 1. Introduction

Diabetes mellitus is with 220.000 deaths per year the eighth leading cause of death in high income countries (World Health Organization (WHO) 2008). In 2007, over 740.000 people in the Netherlands were suffering from diabetes and this number is expected to grow to 1.3 million people in 2025 (National Institute for Public Health and the Environment (RIVM) 2010). Worldwide approximately 285 million people had the disease in 2010 and this number will increase till 438 million in 2030 (World Diabetes Foundation (WDF) 2010). In 2000, diabetes was most prevalent in India with 31.7 million cases. China (20.8 million cases) and the United States (17.7 million cases) were on the second and third place. Diabetes also has a great economic impact on the individual, nation healthcare system and economy (International Diabetes Federation (IDF) 2010).

Type 1 diabetes accounts for 5% of all cases of diabetes worldwide. Of this 5% the vast majority are children. In type 1 diabetes the body does not produce insulin (American Diabetes Association (ADA) 2010). The disease has a strong genetic component, inherited mainly through the HLA complex but the exact cause is unknown. Most likely there is an environmental trigger in genetically susceptible people that causes an immune reaction. The body's white blood cells mistakenly attack the insulin-producing pancreatic  $\beta$ -cells (U.S. National Library of Medicine 2011). Putative environmental triggers include viruses (e.g. enteroviruses), environmental toxins (e.g. nitrosamines) or foods (e.g. early exposure to cow's milk proteins, cereals or gluten) (Daneman D 2006). This 'food' trigger explains why type 1 diabetes is less common in people who were breastfed and in those who first ate solid foods at later ages (Sadauskaitè-Kuehne V et al. 2004; American Diabetes Association (ADA) 2010).

People with type 1 diabetes also have an increased risk of developing some serious and life threatening complications. This involves acute complications, like hyperglycaemia and hypoglycaemia which can lead to a coma, but also chronic complications (National Institute for Public Health and the Environment (RIVM) 2007). Chronic complications can be subdivided into macrovascular and microvascular complications. Cardiovascular disease is the major macrovascular complication and includes mainly myocardial infarction and stroke (American Diabetes Association (ADA) 2010). The risk for cardiovascular disease, is 4-8

times higher for people with type 1 diabetes (Soedamah-Muthu SS et al. 2006). The major microvascular complications are diabetic nephropathy, diabetic neuropathy and diabetic retinopathy (American Diabetes Association (ADA) 2010). Of the patients with type 1 diabetes approximately 29% develop persistent microalbuminuria (urinary albumin excretion rate between 30 and 300 mg/24 h) after 20 years. Of these 29%, 34% progressed further to persistent macroalbuminuria (urinary albumin excretion rate > 300 mg/24 h). Persistent microalbuminuria is a risk factor for the development of diabetic nephropathy. Microalbuminuria can be seen as an early marker of diabetic kidney disease (Hovind P 2004). Also retinopathy is a common microvascular complication. The 25-year cumulative incidences of any visual impairment and severe visual impairment are 13% and 3%, respectively. Diabetic retinopathy is an important cause of visual impairment (Klein R et al. 2010). Finally the high incidence of lower extremity amputations also stresses how serious the complications of type 1 diabetes are. The overall 25-year incidence of lower extremity amputations is 10.1% in 943 American type 1 diabetic patients (Sahakyan K et al. 2011). These complications account for the major morbidity and mortality associated with type 1 diabetes, so it is very important to treat them (Daneman D 2006).

In type 1 diabetes, special attention is paid to balancing the insulin dose with episodes of activity and the quantity and timing of food intake to prevent acute episodes of hypoglycaemia and hyperglycaemia (Franz MJ et al. 2003). This is important because these acute complications can lead to a coma, but also because a high blood glucose concentration (glycosylated hemoglobin (HbA1c)  $\geq 7\%$ ) in people with diabetes increases the risk for macrovascular as well as microvascular complications. Other risk factors for these chronic complications are smoking, obesity, physical inactivity, high blood pressure and high cholesterol levels. Also people with a longer history of diabetes have a higher risk (National Institute for Public Health and the Environment (RIVM) 2007). Furthermore it is important to realise that the microvascular complications lie on the pathway between diabetes and cardiovascular disease. Nephropathy for example is an important risk factor for cardiovascular disease in people with type 1 diabetes (Jensen T et al. 1987).

Recent studies have shown that people with type 1 diabetes eat a more atherosclerosis-prone diet. This includes a high intake of energy from saturated fat and a low intake of fiber, fruits and vegetables, which could increase the risk of the development of atherosclerosis. An atherogenic diet may contribute to the risk of cardiovascular disease (Øverby NC et al. 2006; Snell-Bergeon JK et al. 2009). It has been demonstrated that 80%-90% of type 2 diabetes and coronary heart disease cases can be prevented by healthy lifestyle behavior with a focus on healthy diet and exercise. (Stampfer et al. 2000; Hu et al. 2001; Yusuf et al. 2004) These studies suggest that there could be a potential role for diet in type 1 diabetes to reduce the risk of cardiovascular disease.

There are more studies suggesting that diet (including alcohol) can play an important role in treating the complications of diabetes (Franz MJ et al. 2003; Franz et al. 2010). Several studies have reviewed nutritional recommendations for people with diabetes (Franz MJ et al. 2003; Toeller M July 2010). But most of these recommendations combine both type 1 as well as type 2 diabetes. Furthermore they are general and not always specific for the different type of complications. An overview of the relationship between diet (including alcohol) and complications in type 1 diabetic patients is lacking. Also the effect of lifestyle (including physical activity and dietary patterns) on complications is still not elucidated for type 1 diabetic patients. Lack of physical activity together with an atherogenic diet could enhance development of complications especially in high risk type 1 diabetic patients.

In the following paragraphs of this bookchapter the literature on associations between diet (including alcohol) and lifestyle and chronic complications in type 1 diabetic patients will be summarized. Since 'diet' and 'lifestyle' are broad terms the focus will be on macronutrients (carbohydrates (including fiber), proteins and fats (including cholesterol), alcohol, physical activity and dietary patterns. The paragraphs are divided by nephropathy, retinopathy and CVD. In the final paragraphs all recommendations on diet and lifestyle in patients with type 1 diabetes will be put in perspective with the current literature.

## **2. Diet, lifestyle and nephropathy**

Eighteen studies reported an association between macronutrients and type 1 diabetic nephropathy. Of these, thirteen reported results for the association between protein and nephropathy. The other five focussed on other dietary macronutrients such as fat, cholesterol or carbohydrate in relation with nephropathy. There were also three studies that reported results for protein as well as carbohydrate or fats and nephropathy. Furthermore one study reported an association between alcohol consumption and nephropathy in type 1 diabetic patients and one study reported an association between physical activity and nephropathy in type 1 diabetic patients. No studies were found examining the effect of glycaemic index/glycaemic load on nephropathy in type 1 diabetic patients.

### **2.1 Macronutrients**

#### **2.1.1 Protein**

Of the thirteen studies that reported an association between protein and nephropathy there were three cross-sectional studies (Toeller M et al. 1997; Riley MD& Dwyer T 1998; O'Hayon BE et al. 2000), one case control study (Möllsten AV et al. 2001), two cohort studies (Jibani MM et al. 1991; Barsotti G et al. 1998), six randomized controlled trials (Brouhard BH& LaGrone L 1990; Zeller K et al. 1991; Dullaart RP et al. 1993; Raal FJ et al. 1994; Hansen HP et al. 1999; Hansen HP et al. 2002) and a pilot study (Percheron C et al. 1995). These will be discussed in the following paragraphs by study design.

The three cross-sectional studies were not consistent in their conclusions on the effect of protein on diabetic nephropathy. O'Hayon et al. (O'Hayon BE et al. 2000) failed to show a significant relationship between dietary protein intake and markers of early nephropathy, other than creatinine clearance. Toeller et al. (Toeller M et al. 1997) found a significant relationship between dietary protein intake and urinary albumin excretion rate (AER). A higher AER was particularly found in people consuming more than 20% of their dietary food energy as protein. Riley et al. (Riley MD& Dwyer T 1998) even found the opposite, a decreased prevalence of microalbuminuria at high relative intakes of protein.

In the case-control study (Möllsten AV et al. 2001) total protein intake was not associated with the presence of microalbuminuria, but a diet including a high amount of fish protein seemed to decrease the risk. Furthermore they could not confirm an association between a high total animal protein intake and having microalbuminuria. In contrast to this finding, Jibani et al. (Jibani MM et al. 1991) found in their cohort study that a predominantly vegetarian diet (low in animal protein) may have an important beneficial effect on diabetic nephropathy without the need for a heavily restricted total protein intake. But they were not able to determine if the reduction in total protein intake rather than the reduction in the fraction of animal origin was primarily responsible for the fall in the fractional albumin clearance. Another (Barsotti G et al. 1998) cohort study showed that a low protein diet has a protective effect on the residual renal function in type 1 diabetic patients.

In conclusion, these studies were not consistent in their conclusions on the effect of protein restriction on type 1 diabetic nephropathy. Furthermore there is not enough evidence for recommendations about the preferred type of dietary protein.

Of the six randomized controlled trials reporting an association between protein and nephropathy (**Table 1**), four have reported a decline in glomerular filtration rate (GFR) during the low protein diet (protein intake of approximately 0.8 g/kg/day) (Brouhard BH& LaGrone L 1990; Dullaart RP et al. 1993; Hansen HP et al. 1999; Hansen HP et al. 2002). In one of these four this decline was greater in the low protein diet group than in the usual protein diet group, but this difference was not significant (Hansen HP et al. 1999). In two studies this decline was greater in the usual protein diet group than in the low protein group (Brouhard BH& LaGrone L 1990; Hansen HP et al. 2002). Among these 2 studies, one (Brouhard BH& LaGrone L 1990) found a decline that was significantly greater in the usual protein group. Another study showed a decline in GFR in the low protein diet group, but did not directly compare this with the usual protein group (Dullaart RP et al. 1993). Only one study (Raal FJ et al. 1994) reported an increase in GFR during the low protein diet, but this increase was not significant. Zeller et al. (Zeller K et al. 1991) used iothalamate clearance and creatinine clearance to assess renal function. The rates of decline in both iothalamate and creatinine clearance were significantly slower in the patients in the study-diet group than in those in the control-diet group.

Five trials reported an effect of protein on albuminuria (Brouhard BH& LaGrone L 1990; Dullaart RP et al. 1993; Raal FJ et al. 1994; Hansen HP et al. 1999; Hansen HP et al. 2002). In three of these five trials there was a decline in albuminuria in the low protein diet group as well as in the usual protein diet group (Dullaart RP et al. 1993; Hansen HP et al. 1999; Hansen HP et al. 2002). Two of these three showed a significant greater decline in albuminuria in the low protein diet group than in the usual protein diet group (Dullaart RP et al. 1993; Hansen HP et al. 1999). The other two trials showed a decline in albuminuria in the low protein diet group and an increase in the usual diet protein group (Brouhard BH& LaGrone L 1990; Raal FJ et al. 1994). One of these (Brouhard BH& LaGrone L 1990) found a significant difference between the diet groups. Furthermore, another (pilot) study (Percheron C et al. 1995) also found a decline in albuminuria and in creatinine clearance. They conclude that moderately (protein intake of approximately 1.2 g/kg/day) rather than severely protein restricted diets (protein intake of approximately 0.8 g/kg/day) should be recommended, because of the lack of compliance with severely protein restricted diets. The only trial (Hansen HP et al. 2002) that determined the effect of dietary protein restriction on survival and progression to end stage renal disease (ESRD) in diabetic nephropathy reported a relative risk of 0.23 (95% CI: 0.07-0.72) for ESRD in patients assigned to a low-protein diet compared with patients assigned to a usual protein diet.

In conclusion, protein restriction (protein intake of approximately 0.8 g/kg/day, **Table 1**) had a positive significant effect on albuminuria, but no effect on GFR was found.

### 2.1.2 Carbohydrate

Two cross-sectional studies (Watts GF et al. 1988; Riley MD& Dwyer T 1998) examined the association between carbohydrates and nephropathy. In one study (Watts GF et al. 1988) type 1 diabetic patients with microalbuminuria consumed a significantly smaller percentage of total energy as carbohydrate compared with patients with normal albumin excretion. In the other study (Riley MD& Dwyer T 1998) no significant association between energy adjusted carbohydrate intake and microalbuminuria was found. This could be due to their

Ref.	Study pop.	Age (mean or range)	Study duration	Exposure	Results	
					Mean protein intake (g/kg/day)	GFR
Hansen (2002) (Hansen HP et al., 2002)	n=82	18-60	4 years	LPD (0.6 g/kg/day) vs. UPD	LPD: 0.89 UPD: 1.02	LPD: mean decline 3.8 ml/min/yr UPD: mean decline 3.9 ml/min/yr
Hansen (1999) (Hansen HP et al., 1999)	n=29	18-60	8 weeks	LPD (0.6 g/kg/day) vs. UPD	LPD: 0.8 UPD: 1.1	LPD: mean decline 8.6 ml/min/1,73m <sup>2</sup> UPD: mean decline 2.5 ml/min/1,73m <sup>2</sup>
Raal (1994) (Raal FJ et al., 1994)	n=22	20-41	6 months	Unrestricted protein diet (>1,6 g/kg/day) vs. moderately protein-restricted diet (0,8 g/kg/day)	LPD: 0.87 UPD: 2.00	LPD: mean increase 3 ml/min/1,73m <sup>2</sup> UPD: mean decline 8 ml/min/1,73m <sup>2</sup>
Dullaart (1993) (Dullaart RP et al., 1993)	n=30	40,8	2 years	LPD (0.6 g/kg/day) vs. UPD	LPD: 0.79	
Zeller (1991) (Zeller K et al., 1991)	n=35	18-60	mean: 34.7 months	LPLP (0.6g/kg/day protein; 500-1000 mg phosphorus) vs. Control diet (1.0 g/kg/day protein; 1000 mg phosphorus)	LPLP: 0.72 Control: 1.08	LPLP: IC: decline of 0.0043 ml/s/mo CC: 0.0055 ml/s/mo Control: IC: decline of 0.0168 ml/s/mo CC: 0.0135 ml/s/mo
Brouhard (1990) (Brouhard BH& LaGrone L 1990)	n=15	18-49	12 months	LPD (0.6 g/kg/day) vs. UPD	LPD: 1.3 UPD: 1.5	LPD: decline 0.28 ml/min/1.73m <sup>2</sup> /mo UPD: decline 0.68 ml/min/1.73m <sup>2</sup> /mo

\* after adjustment for MAP (mean arterial pressure) and diabetes duration

GFR: glomerular filtration rate; LPD: low protein diet; UPD: usual protein diet; LPLP: low protein, low phosphorus; CC: creatinine clearance

Table 1. Randomized controlled trials; protein and diabetic nephropathy

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study design (cross-sectional), due to a substantial measurement error in the food frequency questionnaires (FFQs) and due to the low response rate (61.2%) for participation.

### 2.1.3 Fat/cholesterol

Four cross-sectional studies reported an association between fat and/or cholesterol and nephropathy (Watts GF et al. 1988; Bouhanick B 1995; Riley MD& Dwyer T 1998; Toeller M et al. 1999<sup>1</sup>). One study (Riley MD& Dwyer T 1998) found no significant association between energy adjusted monounsaturated fat intake or energy adjusted polyunsaturated fat intake and microalbuminuria, but reported a positive association between usual dietary saturated fat intake and microalbuminuria. Another study (Watts GF et al. 1988) found a significant positive association between total fat intake and microalbuminuria. Another study (Bouhanick B 1995) examined the relationship between fat intake and glomerular hyperfiltration (GFR > 173 ml/min/1.73m<sup>2</sup>), a marker for diabetic nephropathy, in type 1 diabetic patients. They found that excess fat intake may contribute to hyperfiltration in type 1 diabetic patients. Finally the fourth study (Toeller M et al. 1999<sup>1</sup>) found a higher intake of cholesterol, total fat and saturated fat in Eastern Europe compared to Southern or North-Western Europe. They also found more frequent acute and chronic complications (including nephropathy) in Eastern Europe people. Since it was a cross-sectional study they could not conclude if this was due to the high intake of cholesterol, total fat and/or saturated fat.

These cross-sectional studies show that there seems to be a detrimental effect of total dietary fat intake as well as saturated fat intake on type 1 diabetic nephropathy. No association between energy adjusted MUFA and energy adjusted PUFA and microalbuminuria was found.

In a case-control study (Möllsten AV et al. 2001), no association between total fat intake and microalbuminuria was found. In a prospective study (Cárdenas C et al. 2004) a progression of nephropathy with greater saturated fatty acid (SFA) consumption and lesser polyunsaturated fatty acid consumption (PUFA) was demonstrated. Specifically with higher SFA-to-PUFA and SFA-to-MUFA ratios. Another prospective cohort study (Lee CC et al. 2010) found an association between PUFA and microalbuminuria. They found that dietary n-3 PUFAs (eicosapentaenoic acid and docosahexaenoic acid) are inversely associated with the degree but not with the incidence of albuminuria in type 1 diabetes (Lee CC et al. 2010).

In conclusion these prospective studies are consistent with the cross-sectional studies about the detrimental effect of saturated fat on type 1 diabetic nephropathy. The effect of total fat intake on nephropathy is still not elucidated. The cross-sectional study of Watts et al. (Watts GF et al. 1988) and the case control study of Möllsten et al. (Möllsten AV et al. 2001) were in contrast with each other. Also the effect of PUFAs on nephropathy is still doubtful, but there seems to be an inverse association between n-3 PUFAs and the degree of albuminuria.

### 2.1.4 Alcohol

In the EURODIAB Prospective Complications Study (Beulens et al. 2008) the association between alcohol and nephropathy was analysed cross-sectionally. They found that moderate alcohol consumers (30-70 g alcohol per week) had a lower risk of diabetic nephropathy, with an odds ratio of 0.36 (95% CI: 0.18-0.71). This association was most pronounced for the consumption of wine.

### 2.1.5 Physical activity

There were no prospective studies on physical activity and type 1 diabetic nephropathy. One cross-sectional study (Kriska AM et al. 1991) found the lowest occurrence of diabetic nephropathy in people being 7+ hours a week physically active (sports and leisure physical activity).

## 3. Diet, lifestyle and retinopathy

Only two studies reported results for the association between macronutrients and type 1 diabetic retinopathy. Furthermore two studies reported an association between alcohol consumption and diabetic retinopathy and one study reported an association between physical activity and diabetic retinopathy. No studies were found examining the effect of glycaemic index/glycaemic load on retinopathy in type 1 diabetic patients.

### 3.1 Macronutrients

In post-hoc analyses (Cundiff DK& Nigg CR 2005) a positive association between total dietary fat, saturated fat and MUFA with retinopathy progression and retinopathy risk factors (mean arterial pressure, LDL/HDL cholesterol ratio, serum triglycerides, HbA1c, body mass index, and insulin utilization) was found. Furthermore, a negative association between carbohydrates and dietary fiber with retinopathy progression and risk factors was found. In addition to this, another cross-sectional study (Toeller M et al. 1999<sup>1</sup>) reported a higher intake of cholesterol, total fat and saturated fat in Eastern Europe compared to Southern or North-Western Europe. They also found more frequent acute and chronic complications (including retinopathy) in Eastern European people. As with nephropathy, they could not conclude if this was due to the high intake of cholesterol, total fat and/or saturated fat.

In conclusion there is limited research on the effect of diet on diabetic retinopathy. The results of the post hoc analyses should be interpreted carefully, since it is a retrospective analysis which can generate hypotheses but not prove them.

#### 3.1.2 Alcohol

In cross-sectional analyses of the EURODIAB Prospective Complications Study (Beulens et al. 2008) moderate alcohol consumers (30-70 g alcohol per week) had a lower risk of diabetic proliferative retinopathy, with an odds ratio of 0.60 (95% CI: 0.37-0.99). This association was most pronounced for the consumption of wine. Another cross-sectional study (Moss SE et al. 1992) examined whether alcohol consumption was associated with type 1 diabetic retinopathy. They found that moderate alcohol consumption was inversely associated with the prevalence of retinopathy (OR=0.49, 95% CI: 0.27-0.92) in patients with type 1 diabetes.

#### 3.1.3 Physical activity

One cross-sectional study (Kriska AM et al. 1991) examined the relationship between physical activity and the occurrence of retinopathy in type 1 diabetic patients. They found no association between physical activity (sports and leisure physical activity) and occurrence of retinopathy.



## 4. Diet, lifestyle and cardiovascular disease

Eight studies reported an association between macronutrients and CVD in type 1 diabetic patients. Of these eight, six are cross-sectional studies (Toeller M et al. 1999<sup>1,2,3</sup>; Helgeson 2006; Øverby NC et al. 2006; Snell-Bergeon JK et al. 2009). Only Strychar et al. (Strychar I et al. 2009) and Georgopoulos et al. (Georgopoulos A et al. 2000) performed a randomized controlled trial. One study reported an association between lifestyle risk factors (including alcohol) and atherosclerosis, which is often the underlying cause of CVD (Bishop et al. 2009). Eight studies reported an association between physical activity and CVD risk factors (Kriska AM et al. 1991; Lehmann R et al. 1997; Fuchsjäger-Mayrl G et al. 2002; Herbst A et al. 2007; Valerio G et al. 2007; Bishop et al. 2009; Trigona B et al. 2010; Seeger JPH et al. 2011), and two studies reported an association with dietary patterns (Gunther ALB et al. 2008; Liese AD et al. 2011). Furthermore no studies were found examining the effect of glycaemic index/glycaemic load on CVD in type 1 diabetic patients.

### 4.1 Macronutrients

Data on the relationship between macronutrients and incident CVD is lacking in patients with type 1 diabetes. Limited information on macronutrients is available from cross-sectional studies. Main focus was on fat, in particularly saturated fat, and fiber and CVD risk factors were used as a proxy for CVD events.

### 4.2 Cross-sectional studies on fat and fiber in relation to CVD

In more detail, one cross-sectional study (Øverby NC et al. 2006) found a higher than recommended percentage of energy intake from fat and saturated fat among type 1 diabetic patients compared with healthy same-age control subjects and a lower than recommended intake of fiber. They conclude that this higher intake of energy from saturated fat and this lower intake of energy from dietary fiber, vegetables and fruits could increase the risk of atherosclerosis, which is often the underlying cause of CVD. Another study (Helgeson 2006) reported a higher than recommended percentage of energy intake from fat and saturated fat among type 1 diabetic patients, but they did not study associations with CVD or CVD risk factors. Another cross-sectional study (Toeller M et al. 1999<sup>2</sup>) found similar associations between dietary fiber and CVD. Higher fiber intake had a protective significant effect against CVD in type 1 diabetic women but not in men. In type 1 diabetic men it leads to positive changes of the serum cholesterol pattern (higher HDL, lower LDL, lower ratio total cholesterol:HDL cholesterol). In another study (Toeller M et al. 1999<sup>3</sup>) a significant increase in energy adjusted total and LDL-cholesterol levels was associated with higher intakes of total fat, saturated fat and cholesterol. This was associated with a higher prevalence of CVD, although after adjusting for dietary fiber intake, these associations were attenuated. A third study by Toeller et al. (Toeller M et al. 1999<sup>1</sup>) found a higher intake of cholesterol, total fat and saturated fat in Eastern Europe compared to Southern or North-Western Europe. They also found more frequent acute and chronic complications (including CVD) in Eastern European people. However, since it was a cross-sectional study they could not conclude if this was due to the high intake of cholesterol, total fat and/or saturated fat. In the CACTI study (Snell-Bergeon JK et al. 2009) found an increased risk of CVD in type 1 diabetic patients eating high amounts of fat and saturated fat. Carbohydrates were negatively correlated with CHD risk factors (higher total cholesterol, LDL cholesterol, obesity, poorer glycaemic control). Furthermore higher intakes of fat and protein were associated with greater odds of coronary artery calcium (CAC), which is a strong predictor for coronary

events approximating CVD risk. The opposite was true for carbohydrate intake, higher intake was associated with a reduced odds of CAC.

In conclusion a higher intake of total fat as well as saturated fat is positively correlated with CVD or CVD risk factors (atherosclerosis and CAC in these studies) and a higher intake of carbohydrate is negatively correlated with CVD or CVD risk factors. Furthermore dietary fiber is independently related to a lower risk for CVD in type 1 diabetic women. Since all these studies were cross-sectional, they could only look at the intake of certain nutrients and the prevalence of CVD or CVD risk factors at a certain time point. They could not conclude if these are related to each other and if the nutrients are responsible for the lower or higher prevalence of CVD.

### 4.3 Randomized controlled trials

Two randomized controlled trials reported an association between macronutrients and CVD (Table 2), but demonstrated conflicting conclusions. In one trial (Strychar I et al. 2009), the authors concluded that a diet lower in carbohydrate and higher in MUFA might be preferable to a diet higher in carbohydrate and lower in MUFA for type 1 diabetic patients. This was solely based on the positive effect on triglyceride (TG) levels and plasminogen activator inhibitor 1 levels (PAI-1) in the first diet. A significant decrease in PAI-1 was found after 6 months in the lower carbohydrate and higher MUFA diet. In the other diet there was a significant increase after 6 months of follow up. PAI-1 is an inhibitor of fibrinolysis, a process that degrades blood clots. A lower level of PAI-1 means less inhibition and more degradation of blood clots, which means a lower chance of developing atherosclerosis. Also a decrease in TG levels was found after 6 months following the low carbohydrate/high MUFA diet, although this decrease was not significant. In the other diet group there was an increase in TG levels, also this increase was not significant. Furthermore they conclude that the lower carbohydrate/higher MUFA diet was only a proper choice for nonobese individuals with weight control since this diet had induced a weight gain of 2% (1.6 kg) after 6 months. The other trial (Georgopoulos A et al. 2000) found exactly the opposite using a crossover design. They found that a diet high in carbohydrates might be preferable to a diet high in MUFA. Mainly because of the higher atherosclerotic risk due to more and bigger very low-density lipoprotein (VLDL) particles in the last diet. Furthermore the TG levels did not significantly differ between the two diets in this study.

In conclusion, these trials show that the effect of carbohydrate or MUFA on cardiovascular disease risk factors in type 1 diabetic patients is still not elucidated. Although they recommend exactly the opposite (higher intake of MUFA preferable vs. higher intake of carbohydrate preferable) they both found that a high MUFA or a high carbohydrate diet did not affect the TG levels. Their conclusions are based on PAI-1 and VLDL levels, which are not such a good predictors for atherosclerosis (and by extension CVD) as TG levels are. Furthermore none of these randomized controlled trials examined the potential positive effect of dietary fiber on CVD or the potential negative effect of saturated fat found in cross-sectional studies.

### 4.4 Alcohol

One cross-sectional study (Bishop et al. 2009) reported findings on the association between alcohol and cardiovascular disease. No significant association was found between alcohol consumption ( $\pm 13.8$  drinks/month) and CAC, a marker of coronary artery atherosclerosis (adjusted OR=0.9, 95% CI: 0.8-1.1,  $p=0.15$ ). The positive effect of moderate alcohol

Ref.	Study pop.	Age (mean or range)	Study duration	Exposure	Results	
					PAI-1 (ng/ml) (mean ± SD)	TG (mmol/l) (mean ± SD)
Strychar (2009) (Strychar I et al., 2009)	n=30	37.9	6 months	diet high in CH/low in fat* vs. diet low in CH/high in fat**	HCLF: change after 6 mo: -12.8 ± 27.0 LCHF: change after 6 mo: + 14.2 ± 24.5	HCLF: change after 6 mo: -12.8 ± 27.0 LCHF: change after 6 mo: + 14.2 ± 24.5
Georgopoulos (2000) (Georgopoulos A et al., 2000)	n=19	22-47	4 weeks	diet high in MUFA*** vs. diet high in CH****		High MUFA: 0.89 ± 0.15 High CH: 0.90 ± 0.15

\* 54-57% CH, 27-30% total fat (10% MUFA)

\*\* 43-46% CH, 37-40% total fat (20% MUFA)

\*\*\* 40% total fatty acids (25% MUFA, 6% PUFA, 9% saturated), 45% CH and 15% protein

\*\*\*\* 24% total fatty acids (9% MUFA, 6% PUFA, 9% saturated), 61% CH and 15% protein

PAI-1: plasminogen activator inhibitor 1; TG: triglycerides; VLDL: very low-density lipoprotein; SD: standard deviation; mean; CH: carbohydrate; MUFA: monounsaturated fatty acid; HCLF: high carbohydrate, low fat; LCHF: low carbohydrate, low fat

Table 2. Randomized controlled trials; diet and cardiovascular disease

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consumption on CVD as in the general population is not confirmed for type 1 diabetic patients in this study. However, this could also be due to the kind of study (cross-sectional) and the fact that markers for CVD were used instead of CVD as endpoint. There are no prospective studies which have addressed the relation between alcohol and CVD in type 1 diabetic patients.

#### 4.5 Physical activity

Of the eight studies that reported an association between physical activity and CVD there were five cross-sectional studies (Kriska AM et al. 1991; Herbst A et al. 2007; Valerio G et al. 2007; Bishop et al. 2009; Trigona B et al. 2010) and three trials (Lehmann R et al. 1997; Fuchsjäger-Mayrl G et al. 2002; Seeger JPH et al. 2011). No prospective cohort studies were found. The studies will be discussed in the following paragraphs by study design.

One study (Kriska AM et al. 1991) examined the relationship between physical activity and the occurrence of CVD in type 1 diabetic patients. They found the lowest occurrence of CVD in people being 4-7 hours a week physical active (sports and leisure physical activity). The other four cross-sectional studies examined an association between physical activity and CVD risk factors. They all found a positive association. Another two studies (Herbst A et al. 2007; Valerio G et al. 2007) found that increased frequency of regular physical activity was associated with lower TG levels. One of these (Herbst A et al. 2007) found besides the positive association with TG levels also a positive significant association between regular physical activity and HDL cholesterol levels. Another study (Trigona B et al. 2010) found that 60 min/day of moderate-to-vigorous physical activity was associated with an enhanced endothelial function in type 1 diabetic patients. Impaired endothelial function is considered as an early sign of atherosclerosis, which is often the underlying cause of CVD. And finally, (Bishop et al. 2009) a significant inverse association between physical activity and CAC, a marker of coronary artery atherosclerosis, was demonstrated.

In conclusion all these studies found a beneficial effect of physical activity on cardiovascular risk factors. However, since all these studies were cross-sectional, they could only look at physical activity and the prevalence of CVD or CVD risk factors at a certain time point. They could not conclude if these are related to each other and if physical activity was responsible for the lower prevalence of CVD.

The three trials reporting an association between physical activity and cardiovascular disease risk factors (**Table 3**) were consistent in their conclusions. They all emphasize an important role for physical activity in type 1 diabetic patients. Two studies (Fuchsjäger-Mayrl G et al. 2002; Seeger JPH et al. 2011) examined the association between physical activity and brachial artery flow-mediated dilation (FMD). Endothelial dysfunction is reflected by an impaired FMD response and is an early sign of atherosclerosis. An increase in FMD was found in type 1 diabetic patients following an exercise training program (endurance sports; on average 2 times a week 60 minutes, **Table 3**). In both trials this increase was significant ( $p=0.038$  and  $p=0.040$  respectively). Two studies (Lehmann R et al. 1997; Fuchsjäger-Mayrl G et al. 2002) examined the impact of physical activity on lipid related cardiovascular risk factors (LDL cholesterol, HDL cholesterol and TG). They both found a decrease in LDL cholesterol levels in the training group, but only in one of these (Lehmann R et al. 1997) this decrease was significant ( $p=0.02$ ). An additional effect was reported in one of these studies (Lehmann R et al. 1997) with a significant increase in HDL cholesterol levels ( $p=0.03$ ) in the training group. No effect of physical activity on TG levels

Ref.	Study pop.	Age (mean)	Study duration	Exposure	Results			
					VO <sub>2max</sub>	FMD (%)	Triglycerides (mmol/L)	
Seeger (2011) (Seeger JPH et al., 2011)	n=7	10.9	18 weeks	18 week exercise training program*	Mean increase: 2.0 ml/kg/min	Mean increase: 4.9		
Fuchsjäger-Mayrl (2002) (Fuchsjäger-Mayrl G et al., 2002)	n=23	37.5	4 months	TrGr: 4 mo exercise training program** C: type 1 diabetic patients following usual lifestyle	TrGr: mean increase: 7.6 ml/kg/min C: mean increase: 0.1	TrGr: mean increase: 3.3 C: mean increase: 0.7	TrGr: mean decline: 0.2 C: mean increase: 0.2	
Lehmann (1997) (Lehmann R et al., 1997)	n=20	33.0	3 months	3 month exercise training program***	Mean increase: 178 ml/min		Mean increase: 0.09	

\* two times a week: first day: 30 min running exercise (intervals) and 30 min group-based activities such as ball games, dance, and stretching; second day: individual exercise session at home involved 30 min of interval running, 30 min of low intensity walking, and 30 min of cooling down (including stretching)

\*\* first 2 weeks: two times a week 1 hour stationary cycling, during the remaining study period three times a week 1 hour stationary cycling

\*\*\* 135 min per week endurance sports (biking, long-distance running, or hiking)

VO<sub>2max</sub>: peak oxygen uptake; FMD: flow mediated dilation; LDL: low-density lipoprotein; HDL: high-density lipoprotein; C: control group

Table 3. Randomized controlled trials; physical activity and cardiovascular disease risk factors



was found in both studies. Furthermore all three studies (Lehmann R et al. 1997; Fuchsjäger-Mayrl G et al. 2002; Seeger JPH et al. 2011) assessed physical fitness by  $VO_{2max}$  (peak oxygen uptake). They all found a positive significant association between physical activity and  $VO_{2max}$ . The relation between physical fitness and CVD was not examined.

In conclusion the three trials show that physical activity improves physical fitness as well as endothelial function in type 1 diabetic patients. A positive effect on lipid related cardiovascular risk factors was only found in one study (Lehmann R et al. 1997).

#### 4.6 Dietary patterns

Two cross-sectional studies reported an association between dietary patterns, in this case the 'Dietary Approaches to Stop Hypertension' (DASH) diet, and CVD risk factors (Gunther ALB et al. 2008; Liese AD et al. 2011). No cross-sectional or prospective studies were found examining the effect of a Mediterranean diet or a Western diet on CVD in type 1 diabetic patients.

One study (Gunther ALB et al. 2008) reported an association between adherence to the DASH diet and hypertension in type 1 diabetic patients. They found that a higher adherence to this diet amongst type 1 diabetic patients was inversely related to hypertension (OR=0.6, 95% CI: 0.4-0.9,  $p=0.007$ ). They did not investigate a possible association between the DASH diet and CVD, but used hypertension as the main risk factor for CVD. Another study (Liese AD et al. 2011) reported a possible association between the DASH diet and other CVD risk factors (total cholesterol, LDL cholesterol, HDL cholesterol, TG, LDL particle density, apolipoprotein B, body mass index (BMI), waist circumference, and adipocytokines) than blood pressure. A significant and inverse association between the DASH diet and LDL/HDL ratio was found. An estimated 0.07 lower LDL/HDL ratio was found in the highest adherence group compared with the lowest adherence group. No significant association was found between LDL particle density, BMI, waist circumference, adipocytokines, or TG and the DASH diet.

In conclusion a positive effect of adherence to the DASH diet on hypertension and LDL/HDL ratio, which are important risk factors for CVD, was found. Unfortunately there were no studies found examining the effect of dietary patterns on CVD events.

### 5. Current recommendations on diet and lifestyle in patients with type 1 diabetes put in perspective

Overall, fiber and saturated fat intake play an important role in type 1 diabetic patients, with a beneficial and detrimental effect on the chronic complications respectively. Many researchers have shown the inappropriate intake of these nutrients in patients with type 1 diabetes. A protein restriction diet helped reduce micro/macro albuminuria in known type 1 diabetic patients with nephropathy, however, the compliance was low. Also moderate alcohol intake and physical activity may have beneficial effects in type 1 diabetic patients. Most of the findings are consistent with the guidelines for type 1 diabetic patients (**Table 4**).

The main limitations are the lack of prospective studies on diet and lifestyle in type 1 diabetics, lack of randomized controlled trials and the limited number of studies on dietary cholesterol, protein, carbohydrates, fat, fiber and no cardiovascular morbidity data. The available studies, with their limitations, all indicate that diet and lifestyle play an important role in preventing chronic complications of type 1 diabetes. To put the findings in the literature in perspective, current nutritional recommendations are evaluated in the



following paragraphs at a macronutrient level. **Table 4** summarizes the nutritional recommendations as well as the lifestyle recommendations for type 1 and type 2 diabetic patients. These recommendations are for all diabetic patients in general, based in the majority of cases on evidence from type 2 diabetic patients.

### 5.1 Carbohydrates

The 'Diabetes and Nutrition Study Group of the European Association for the Study of Diabetes' (DNSG EASD) guidelines for persons with type 1 and type 2 diabetes (**Table 4**) recommend that the most appropriate intake of carbohydrates consists of vegetables, legumes, fruits, wholegrain foods and naturally occurring foods rich in fiber. The fiber intake should be ideally  $\approx 20$  g/1000 kcal/day. Cross-sectional data of the EURODIAB Complications Study showed an inverse association between fiber and LDL cholesterol and a positive association between fiber and HDL cholesterol. In addition dietary fiber was inversely and significantly related to CVD (Toeller M et al. 1999<sup>2</sup>). This effect was already found with a fiber intake of approximately 8.1 g/1000 kcal, which is below the recommended intake. The average fiber intake in type 1 diabetic patients is 8.1 g/1000 kcal, but the recommended intake is 20 g/1000 kcal. Recommendation was only achieved in 0.4% of the type 1 diabetic population (Toeller M et al. 1996). Data from the EURODIAB Prospective Complication Study on fiber intake measured at baseline by 3-day food diaries and presented by each center is given in **Figure 1**. As seen in this figure, even the 10 g/1000 kcal recommended fiber intake by the 'American Diabetes Association' (ADA) was hardly achieved by type 1 diabetic patients. Only Finnish type 1 diabetic patients achieved the ADA fiber recommendation of 10 g/1000 kcal (**Figure 1**). Keeping in mind that these samples are clinic based and not population based and that these figures may not exactly reflect the current nutritional intake, however it gives an indication of the status on fiber intake. Although positive effects were already found on CVD with a fiber intake of 8.1 g/1000 kcal, we assume that effects could be probably even higher when recommended levels of fiber intake are reached. Unfortunately, this positive effect of fiber on CVD and CVD risk factors was only found in cross-sectional studies. This makes it very difficult to distinguish cause and effect. Further research in prospective studies or randomized controlled trials is needed to ascertain the role of fiber in CVD.

DNSG EASD do not recommend a low carbohydrate diet for type 1 and type 2 diabetic patients (**Table 4**). A low carbohydrate diet does not produce beneficial health effect. It is more acceptable to avoid too much foods high in fast available carbohydrates, foods high in fat and cholesterol. An earlier quote (Helgeson 2006) expressed this precisely: 'families of adolescents with diabetes may be more concerned that the sugar in candy is going to translate into high blood glucose levels today than that the fat in potato chips will translate into cardiovascular disease in 10 years'.

### 5.2 Fat

The DNSG EASD guidelines for dietary fat for persons with type 1 and type 2 diabetes recommend a saturated and trans-unsaturated fatty acid consumption of <10% of the total energy intake (<8% if LDL cholesterol is elevated). Total fat intake should not exceed 35% of total energy and dietary cholesterol should be <300 mg/day (**Table 4**). Saturated fat is an important risk factor for diabetic nephropathy, diabetic retinopathy as well as CVD (Riley



MD& Dwyer T 1998; Toeller M et al. 1999<sup>3</sup>; Cárdenas C et al. 2004; Cundiff DK& Nigg CR 2005). The recommended intake is <10% of the total energy intake which was only achieved by a small minority (14%) (Toeller M et al. 1996). Data from the EURODIAB Prospective Complication Study on saturated fatty acid intake measured at baseline by 3-day food diaries and presented by each center is given in **Figure 2**. The even lower saturated fatty acid recommendation of <7% total energy of the ADA was not achieved by any of the centers (**Figure 2**). All centers indicated in **Figure 2** exceed the recommendation of <7% saturated fat of the total energy intake. Type 1 diabetic patients from Italy had the lowest intake of saturated fatty acids, but this intake was still too high (**Figure 2**). Again, keeping in mind that these samples are clinic based and not population based and that these figures may not exactly reflect the current nutritional intake.

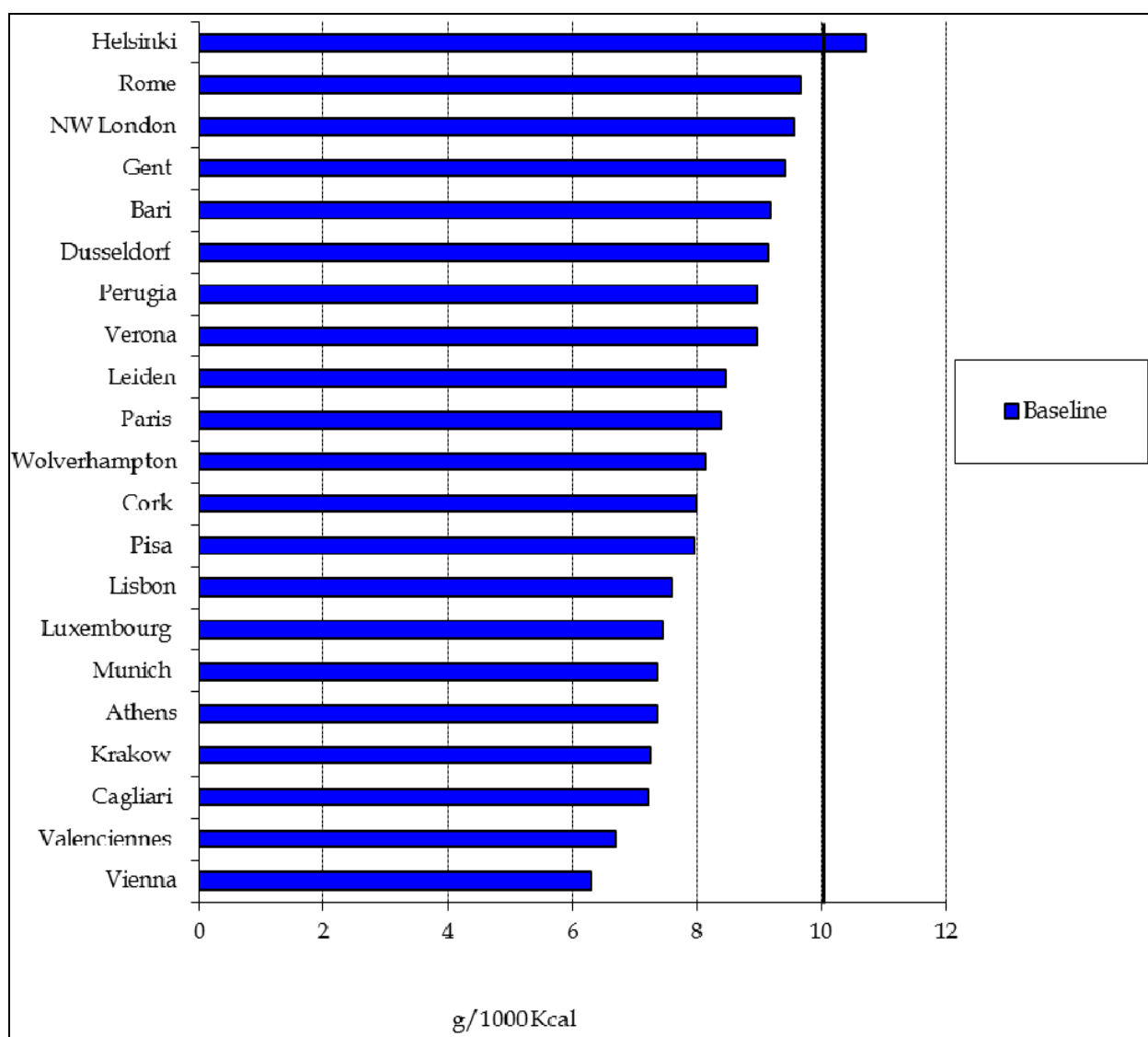


Fig. 1. Mean fiber intake in 1102 individuals with type 1 diabetes across Europa (Toeller M, Soedamah-Muthu 2011)

Furthermore the DNSG EASD guidelines recommend oils rich in MUFA (10-20% total energy) and that PUFA should not exceed 10% of total energy intake (**Table 4**). There were

only a few studies examining the effect of MUFA or PUFA on chronic complications in type 1 diabetic patients. A positive association was found between MUFA and retinopathy (Cundiff DK& Nigg CR 2005) but no association was found between MUFA and PUFA and microalbuminuria (Riley MD& Dwyer T 1998). These conclusions are based on post-hoc analyses and a cross-sectional study respectively and should therefore be interpreted carefully. Also the conclusion of Strychar et al. (Strychar I et al. 2009) to recommend a diet higher in MUFA and lower in carbohydrate for nonobese type 1 diabetic individuals to reduce CVD risk factors is doubtful. Their conclusion is based on PAI-1 and VLDL levels, which are not such a good predictors for atherosclerosis (and by extension CVD) as TG levels are. And a high MUFA diet did not alter TG levels. Furthermore, the small study population of 30 subjects limits the power of their conclusions. In order to make accurate recommendations concerning MUFA and PUFA intake for type 1 diabetic patients more research with more participants (preferably in a prospective study) is needed.

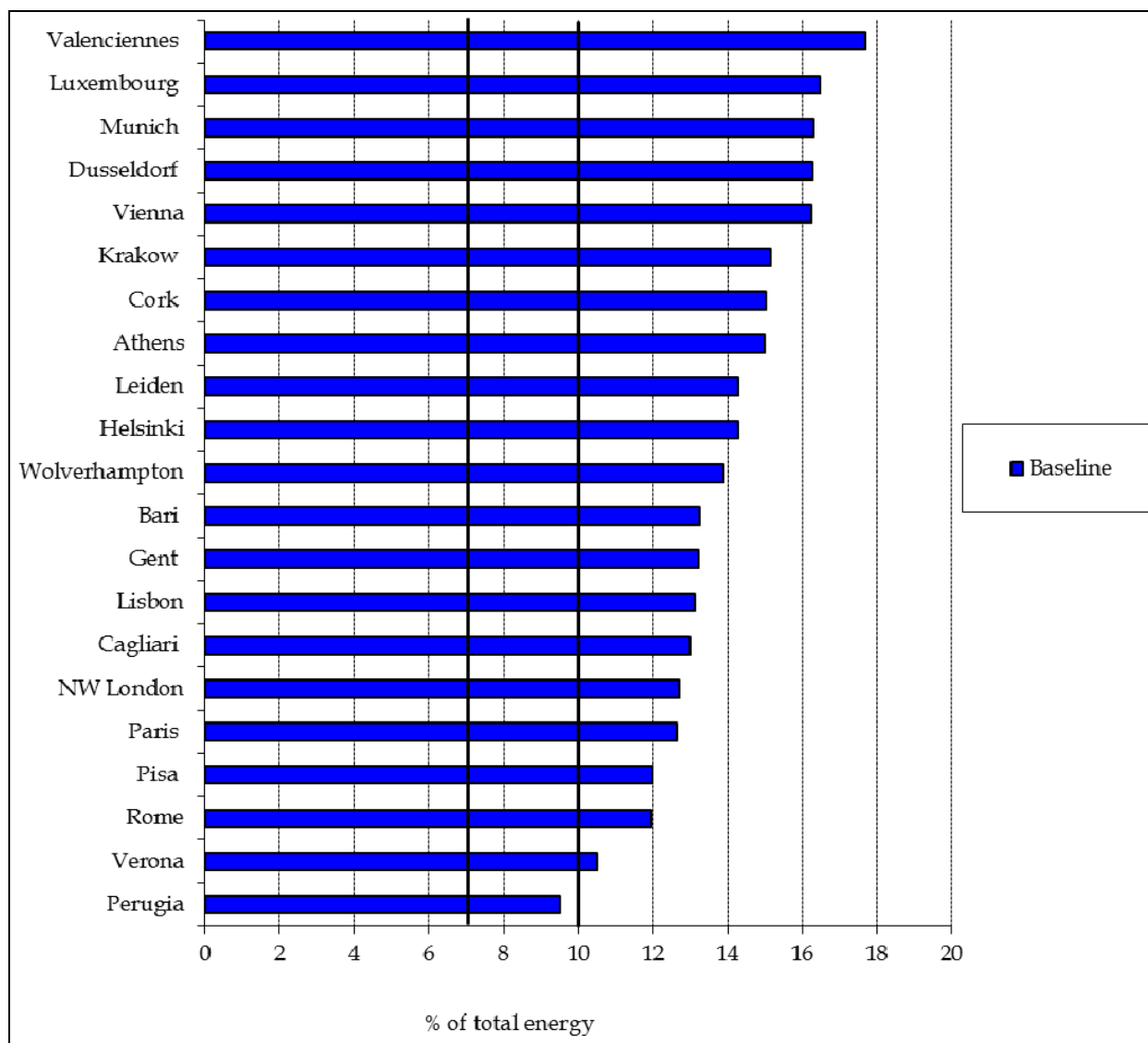


Fig. 2. Mean saturated fatty acid intake in 1102 individuals with type 1 diabetes across Europe (Toeller M, Soedamah-Muthu 2011)

The recommendation of the DNSG EASD to consume 2-3 servings of oily fish/week and plant sources of n-3 fatty acids (**Table 4**) is consistent with the findings in studies specific for type 1 diabetes. The prospective cohort study of Lee et al. (Lee CC et al. 2010) found that dietary n-3 PUFAs (eicosapentaenoic acid and docosahexaenoic acid) are inversely associated with the degree but not with the incidence of albuminuria in type 1 diabetes. A hypothesis is that n-3 PUFAs decrease urinary AER via anti-inflammatory mechanisms. It decreases lipopolysaccharide-induced nuclear factor-kB (NF-kB) activation and monocyte chemoattractant protein (MCP)-1 expression in human renal tubular cells (Lee CC et al. 2010). Further prospective studies and randomized controlled trials are needed to confirm this hypothesis.

### 5.3 Protein

With regards to protein, the DNSG EASD guidelines recommend an intake of 0.8 g/kg normal body weight in patients with type 1 diabetes and established nephropathy. There are no firm recommendations regarding protein intake for type 1 diabetic patients with incipient nephropathy. An intake of 10-20% of total energy is recommended for patients with no evidence of nephropathy (**Table 4**). The recommendation for protein intake is most important for patients with diabetic nephropathy. The guideline of a restricted protein diet which contains 0.8 g/kg normal body weight for type 1 diabetic patients with established nephropathy was demonstrated by previous research. Several randomized controlled trials showed that protein normalization (protein intake of approximately 0.8 g/kg/day, **Table 1**) had a positive significant effect on albuminuria, although no effect on GFR was found (Brouhard BH & LaGrone L 1990; Zeller K et al. 1991; Dullaart RP et al. 1993; Raal FJ et al. 1994; Hansen HP et al. 1999; Hansen HP et al. 2002). Even a relative risk of 0.23 (95% CI: 0.07-0.72) was found for ESRD in patients assigned to a low protein diet compared with patients assigned to a usual protein diet (Hansen HP et al. 2002). A hypothesis is that excessive protein intake causes renal vasodilatation and glomerular excessive perfusion leading to a raised glomerular transcapillary hydraulic pressure gradient ending in proteinuria and glomerular damage, conversely, will prevent kidney damage (Percheron C et al. 1995). So, indeed protein restriction is beneficial for type 1 diabetic patients with established nephropathy. However, we have to mention that although this beneficial effect of a restricted protein intake was found in randomized controlled trials, the sample size of these trials were really small (maximum of 82 people). Furthermore, we have to consider the feasibility of a protein intake of 0.8 g/kg/day. Percheron et al. (Percheron C et al. 1995) showed that even with this intake the compliance is poor. Further studies with a larger sample size are needed to find a cutoff point for protein intake which would still have a positive effect on diabetic nephropathy and its feasibility.

### Alcohol

The DNSG EASD guidelines for alcohol for persons with type 1 and type 2 diabetes recommend a moderate use up to 10 g/day for women and up to 20 g/day for men (**Table 4**). In prior studies, moderate alcohol consumers (30-70 g alcohol per week) had a lower risk of diabetic nephropathy (OR=0.36, 95% CI: 0.18-0.71) and diabetic retinopathy (OR=0.60, 95% CI: 0.37-0.99) in patients with type 1 diabetes (Beulens et al. 2008). Alcohol has favourable effects on HDL-cholesterol, inflammation and inhibition of platelet aggregation

(Beulens et al. 2008). Because of this favourable effects we expect a beneficial effect on CVD, however to date no association was found between alcohol and CVD in type 1 diabetes patients (Bishop et al. 2009). In this cross-sectional study, markers for CVD were used instead of CVD as endpoint. Also the association between alcohol and diabetic nephropathy and diabetic retinopathy was only observed in cross-sectional studies. So the current recommendations for alcohol are confirmed by research in type 1 diabetes, but only based on cross-sectional studies, and especially for the association between alcohol and CVD in type 1 diabetic patients more research is needed.

#### 5.4 Physical activity

There are no specific guidelines concerning physical activity for type 1 diabetic patients. The guidelines mentioned in **Table 4** are only for type 2 diabetic patients. However, it was shown that the guidelines for type 2 diabetic patients are also applicable for type 1 diabetic patients. Several randomized controlled trials (**Table 3**) showed that physical activity (endurance sports; on average 2 times a week 60 minutes) improves physical fitness as well as endothelial function in type 1 diabetic patients (Lehmann R et al. 1997; Fuchsjäger-Mayrl G et al. 2002; Seeger JPH et al. 2011). Especially the improvement in endothelial function is important since endothelial dysfunction is an early sign of atherosclerosis, which is often the underlying cause of CVD. Also a positive effect on lipid related cardiovascular risk factors was found in one study (Lehmann R et al. 1997). However, also this conclusion should be interpreted carefully. Although the evidence is gained from randomized controlled trials, the conditions of these trials are really disappointing. They had a maximum sample size of 23 people, and a minimum sample size of only 9 people. The follow-up period was relatively short, up to four months. The studies of Lehman et al. (Lehmann R et al. 1997) and Seeger et al. (Seeger JPH et al. 2011) not even used a control group. Furthermore CVD risk factors were used instead of CVD as endpoint. So the studies are in agreement with the guidelines but more research in better performed randomized controlled trials is needed to confirm this positive effect of physical activity on CVD in type 1 diabetic patients.

## 6. Conclusion

A diet high in fiber, low in saturated fat, moderate in protein intake with moderate alcohol consumption as well as physical activity can be recommended for type 1 diabetic patients to prevent complications. In spite of the lack of large robust prospective studies, using the available evidence, we can conclude that diet as well as lifestyle could play an important role in preventing longterm complications of type 1 diabetes.

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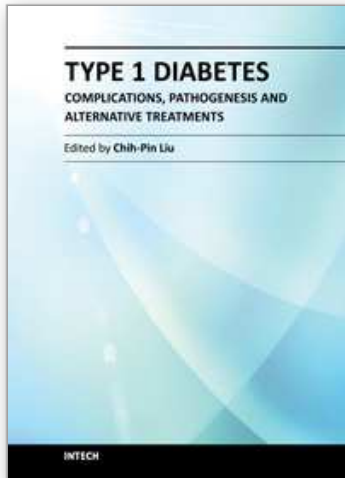
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## **Type 1 Diabetes - Complications, Pathogenesis, and Alternative Treatments**

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This book is intended as an overview of recent progress in type 1 diabetes research worldwide, with a focus on different research areas relevant to this disease. These include: diabetes mellitus and complications, psychological aspects of diabetes, perspectives of diabetes pathogenesis, identification and monitoring of diabetes mellitus, and alternative treatments for diabetes. In preparing this book, leading investigators from several countries in these five different categories were invited to contribute a chapter to this book. We have striven for a coherent presentation of concepts based on experiments and observation from the authors own research and from existing published reports. Therefore, the materials presented in this book are expected to be up to date in each research area. While there is no doubt that this book may have omitted some important findings in diabetes field, we hope the information included in this book will be useful for both basic science and clinical investigators. We also hope that diabetes patients and their family will benefit from reading the chapters in this book.

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