J. Cardiovasc. Dev. Dis. **2014**, *1*, 201-213; doi:10.3390/jcdd1030201

OPEN ACCESS

Journal of
Cardiovascular
Development and Disease

ISSN 2308-3425

www.mdpi.com/journal/jcdd

Review

Effects of Dietary Macronutrients on Plasma Lipid Levels and the Consequence for Cardiovascular Disease

Emilie Daoud [1], Celena Scheede-Bergdahl [2] and Andreas Bergdahl [1,*]

[1] Department of Exercise Science, Concordia University, Montreal, QC, H4B 1R6, Canada; E-Mail: emiliedaoud@live.ca

[2] Department of Kinesiology & Physical Education, McGill University, Montreal, QC, H2W 1S4, Canada; E-Mail: celena.scheede@mcgill.ca

* Author to whom correspondence should be addressed; E-Mail: andreas.bergdahl@concordia.ca; Tel.: +1-514-848-2424 (ext. 3372); Fax: +1-514-848-8681.

Received: 4 June 2014; in revised form: 19 September 2014 / Accepted: 25 September 2014 / Published: 10 October 2014

Abstract: Despite gaining focus, cardiovascular disease (CVD) remains the leading cause of death worldwide. Health promotion agencies have traditionally recommended diets that are low in fat in order to reduce CVD risk however, much debate remains about which dietary approaches are the most efficient for effective disease prevention. Common markers of CVD include elevated plasma triglycerides (TG) and low-density lipoprotein (LDL) cholesterol levels, as well as reduced high-density lipoprotein (HDL) cholesterol levels. While weight loss alone can significantly reduce markers of CVD, manipulating dietary macronutrient content contributes to the beneficial effects of weight loss and furthers the improvement of lipid profiles even without the alteration of total caloric intake. Considering the recent attention to diets that are low in carbohydrates rather than fat, it remains to be elucidated the beneficial effects of each diet type when establishing new recommendations for CVD prevention. This review aims to examine the effects of different macronutrient compositions on lipid markers, thus providing insight into the potential roles of various diet types in the targeted prevention against CVD.

Keywords: plasma lipid levels; cardiovascular disease (CVD); high fat diet; low carbohydrate diet; macronutrients; HDL; LDL; VLDL

1. Background

Cardiovascular disease (CVD) is one of the leading causes of morbidity and mortality worldwide, accounting for approximately 30% of all deaths, as well as placing a significant financial burden on existing health care systems [1,2]. Research targeted at understanding the development and progression of CVD has maintained prominence over the years, however, much debate remains about which clinical approaches are most efficient for its prevention. Rather than using the more traditional approach of weight loss alone to lower the risk of CVD, scientists have begun focusing on nutritional composition as an effective intervention. Recently, research has been directed towards understanding different dietary compositions and their impact on lipid profiles and markers of CVD risk. Based on these trends, many organizations (such as the American Heart Association) are providing dietary guidelines that endorse the higher consumption of whole grains and complex carbohydrates, vegetables and low fat dairy products. Also recommended is the consumption of foods which are lower in fat content, suggesting lean meats such as poultry/fish over red meat, and unsaturated fats over saturated and the avoidance of *trans*-unsaturated fats [3,4]. While low-fat diets such as these are highly recommended for individuals at risk of developing cardiovascular complications, it has become unclear whether these diets in fact improve lipid profiles and lower risk of developing CVD.

Common markers of CVD include elevated levels of triglycerides (TG), low-density lipoprotein (LDL) and cholesterol [5–7]. Decreases of 1 mmol/L in plasma TG and LDL cholesterol levels are associated with a 22.5% and 28% reduction in relative risk of CVD deaths and 29.5% and 26.6% decrease in relative risk of coronary heart disease events, respectively, in populations with and without coronary heart disease [8]. Additionally, high levels of LDL cholesterol and low levels of high-density lipoproteins (HDL) cholesterol (ratio) have been related with coronary events [9]. Increases in HDL cholesterol alone have been found to be insufficient to reduce the risk of CVD-related events or death [10], suggesting that factors such as serum TG and LDL cholesterol, as well as other elements such as apolipoprotein B (ApoB) and apolipoprotein C-III (ApoC-III) content in very-low density lipoprotein (VLDL) cholesterol may be more crucial in assessing CVD risk [11]. In principle, abnormal lipid profiles result in damage to the endothelial cells. This impairment leads to endothelial dysfunction, diminished ability for vasodilation and ultimately allows lipids to penetrate the endothelial layer. This results in the initiation of an oxidative and inflammatory cascade that culminates in the development of plaque deposits. Subsequently, these plaques begin to calcify and, over time, become prone to rupture, a phase which oftentimes results in a deadly blood clot.

2. Lowering CVD Risk: Will Only Weight Loss Do?

Weight loss alone, induced by restricted caloric intake with or without increased physical activity, can reduce cardiovascular risk by decreasing plasma TG levels and increasing HDL cholesterol [12]. Several studies have found similar weight reduction when following either low-fat (10–30% of energy from fat) or low-carbohydrate (4–45% of energy from carbohydrates) isocaloric diets [13], as well as restricted-calorie, low-fat and low-carbohydrate diets that were either low (15% of total energy intake) or high (25% of total energy intake) in protein content [14]. These findings suggest that caloric restriction, rather than macronutrient content, may play a more important role in determining weight

loss. However, some diets appear to be as efficient at reducing body weight in the absence of caloric restriction: for example, a non-restricted low-carbohydrate diet (20–120 g of carbohydrates per day) had similar effects on body weight when compared to a restricted-calorie, low-fat (30% of total energy intake from fat) and Mediterranean-style (a diet contributing ≤35% of energy from fat, with an emphasis on vegetables, poultry and fish) diets [15]. Additional studies have reported significant reductions in body weight with diets low and very-low in carbohydrate content (a diet contributing 10% of energy) [16–18], while others have found that low-fat diets [19] and high-protein diets [20] were significantly more effective at reducing body weight.

While weight loss alone, induced by caloric restriction or a change in diet, can reduce risk of CVD, manipulating dietary macronutrient content has been shown to improve blood lipid profiles even in the absence of weight loss. For example, even though subjects who followed a restricted carbohydrate diet started to regain weight after 6 months, the residual effects of carbohydrate restriction on blood lipids (HDL and triglycerides) levels were detectable for up to 2 years [15]. Another study that compared the effects of dietary macronutrient content (3.5% protein, 56.0% fat and 9.6% carbohydrate *versus* 22.0% protein, 25.0% fat and 55.7% carbohydrate) found that the high fat/low carbohydrate diet resulted in greater improvements in blood lipids and systemic inflammation when compared to the low fat/high carbohydrate, even though there were no detectable differences in body weight between the two diets [21].

Many reports have found beneficial effects of low-fat diets on blood lipid profiles: a recent meta-analysis that included 32 studies, with follow-ups of 12 months or more, found that low-fat diets, where fat intake accounted for 30% or less of total energy, had significantly greater long-term (≥12 months) reductions in LDL cholesterol compared to high-fat diets, where fat intake accounted for more than 30% of total energy [22]. Other low-fat diets, including Dietary Approaches to Stop Hypertension (DASH)-style diets, which are promoted by the National Heart, Lung, and Blood Institute, have similarly been found to lower risk of stroke and coronary heart disease [23], and to significantly lower levels of total, LDL, and HDL cholesterol compared to control diets (approximately 50% of energy intake from carbohydrates, 37% from fat, and 14% from protein); [24] and regular, unmonitored diets [25]. While reductions in total and LDL cholesterol are beneficial for CVD risk, lower levels of HDL cholesterol is also considered a risk factor for the development of CVD. Furthermore, studies have reported significant increases in levels of VLDL cholesterol following low-fat diets [26], which are associated with cardiovascular events [11]. Despite the growing interest in the effects of macronutrient content on blood lipid profiles, more research needs to be conducted in order to gain further insight into the effectiveness of these dietary interventions.

In contrast, VLDL cholesterol levels were found to be significantly reduced following a very-low-carbohydrate diet (60% of energy from fat, 30% from protein, and 10% from carbohydrates) for 4 weeks when compared to levels following 4 weeks of a low-fat diet (25% of energy from fat, 20% from protein, and 55% from carbohydrates; [18]). Additionally, a 12-week diet of high-fat, low-carbohydrate content (60% fat, 35% protein, and ≤40 g/day carbohydrates) led to greater improvements in blood lipid profiles by decreasing TG levels and increasing HDL cholesterol in comparison to a low-fat, high-carbohydrate diet (25% fat, 15% protein, and 60% carbohydrates; [21], which is in agreement with past work [14,15]. Conversely, additional groups have also reported increased levels of LDL cholesterol following low-carbohydrate and high-fat diets [16,22], whereas others reported initial increases in LDL cholesterol in individuals following diets low in carbohydrate

content when compared to those following diets low in fat content, but there were no significant differences after 6 and 12 months follow-up [27].

Research suggests that low-carbohydrate and low-fat diets may produce similar results in the long term. For example, a meta-analysis of 23 randomized controlled studies found that low-carbohydrate (≤45% of energy intake) and low-fat (≤30% of energy intake) diets both reduced total cholesterol, LDL cholesterol and TG levels, and increased HDL cholesterol after interventions that were 6 months or longer, with both diets similarly reducing body weight [13]. Other studies have also reported improvements in lipid profiles following both types of diets [20]. Thus, both types of diets have both positive and negative effects on blood lipid profiles. Low-fat diets generally appear to reduce total cholesterol including LDL and HDL cholesterol, and increase VLDL cholesterol, while low-carbohydrate diets appear to reduce TG levels, increase HDL and LDL cholesterol as well as lower VLDL cholesterol. However, both types of diets may continue to have beneficial effects over time and lead to similar results on blood lipid profiles.

3. Lipid Profile Patterns

Two distinct phenotypes (see Figure 1) in relation to lipid profiles have been observed: pattern A, which is associated with large, buoyant LDL particles (LDL I and II particles), and pattern B, which is associated with small, dense LDL particles (LDL III and IV particles) as well as an increased risk of myocardial infarction compared to individuals with pattern A. These phenotypic differences appear to be linked to a specific genetic locus, suggesting that CVD is partly heritable [28]. No associations between LDL diameter patterns and smoking, diabetes, or hypertension were observed in this sample [29]. However, other studies have reported positive associations between levels of LDL III particles and body mass index (BMI), particularly in men, levels of LDL III and age in both men and women, as well as levels of LDL I particles and alcohol consumption [30]. Individuals with a pattern B lipid profile were also found to be associated with higher levels of plasma TG and very-low-density lipoprotein (VLDL) and intermediate-density lipoprotein (IDL), as well as with lower levels of HDL cholesterol [29], further supporting the link between this phenotype and CVD risk.

Lipid profile patterns can also be affected by dietary changes. For example, a diet contributing 24% energy from low-fat for 6 weeks led to over 40% of individuals who originally had pattern A switching to pattern B (see Figure 2) [26,31]. In a follow-up study (see Figure 3), a third of individuals who had maintained a stable pattern A after the diet with a contribution of 24% of energy from fat, switched to a pattern B following 10 days of a very-low-fat diet (10% contribution of total energy) [26].

In addition, the diet composed of 10% fat, in comparison to a regular diet where approximately 35% of the total energy came from fat, was associated with higher levels of CVD risk factors. Specifically, the 10%, very-low-fat diet resulted in increased TG levels, overall mass of VLDL particles and small, dense atherogenic LDL III and IV particles, all of which are associated with an increased CVD risk. In addition, the mass of large LDL I and small IDL particles, which are less atherogenic than dense particles, was decreased following this diet. These findings suggest that diets with low levels of fat intake, but a higher content of carbohydrates, are associated with a more deleterious lipid profile, even in individuals who previously showed no signs of elevated risk. However, the effects of these diets on lipid profile phenotypes in the long-term remain unclear.

While traditional risk factors for CVD have been assessed in the literature, research suggests that certain apolipoproteins that become part of cholesterol-carrying lipoproteins may be more important markers for CVD risk. For example, elevated concentrations of apolipoprotein B (ApoB)-containing particles, and ApoC-III content in LDL and VLDL particles are strong predictors of atherosclerosis, independent of other known risk factors and CVD-related events [11,32,33]. In regards to these markers, diets low in carbohydrate content may be more efficient at decreasing concentrations of these apolipoproteins in plasma [34]. However, research suggests that the quality, rather than the quantity, of dietary fat may be more crucial in determining overall CVD risk [35].

Figure 1. A schematic image of the low density lipoprotein (LDL) subtype patterns. Low density lipoprotein particles vary in size and density, and studies have shown that small dense LDL particles, called *Pattern B*, equates to a higher risk factor for CVD than does a pattern with more of the larger and less-dense LDL particles (*Pattern A*).

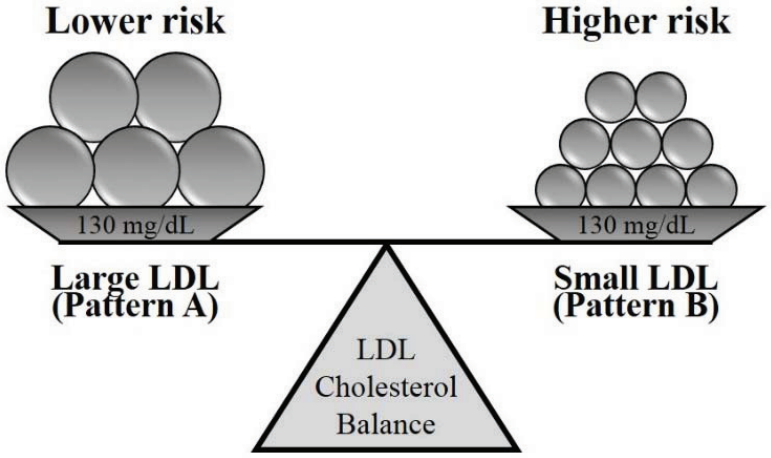


Figure 2. Distribution of LDL peak particle densities determined by analytic ultracentrifugation in 238 men consuming high-fat (40–46% of energy from fat) and low-fat (20–24% of energy from fat) diets. White bars represent subjects with LDL subclass phenotype A and shaded bars subjects with LDL subclass phenotype B. Reprinted with permission [26].

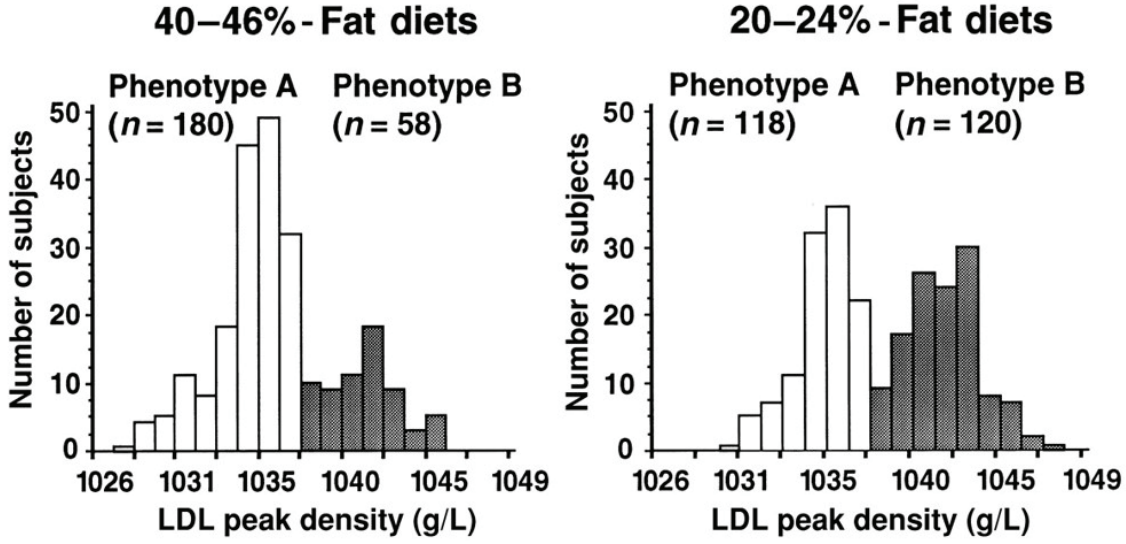
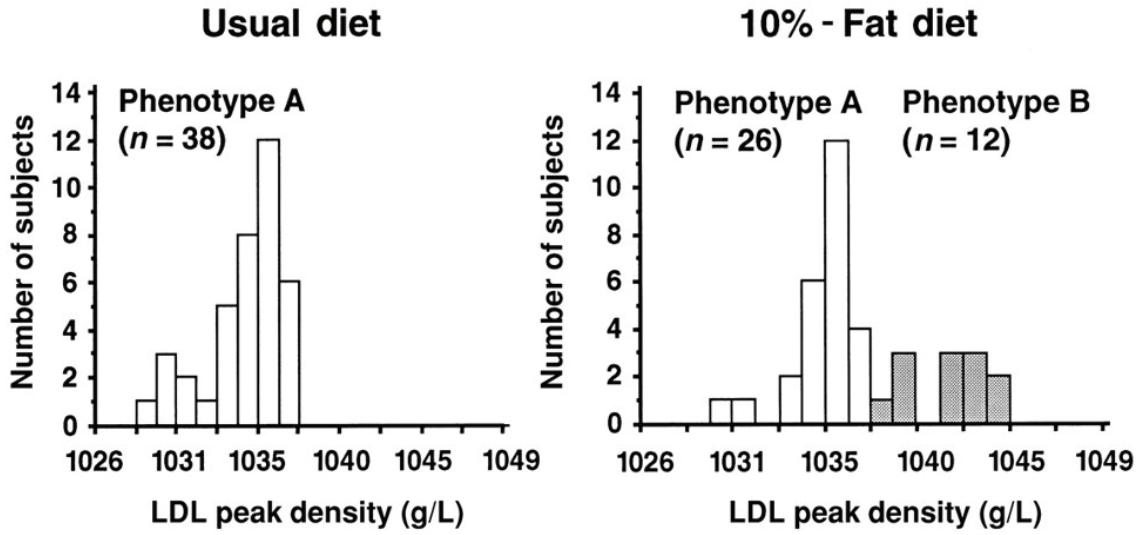


Figure 3. Distribution of LDL peak particle densities determined by analytic ultracentrifugation in 38 men consuming their usual diet (<32% fat) and a 10% fat diets. White bars represent subjects with LDL subclass phenotype A and shaded bars subjects with LDL subclass phenotype B. Reprinted with permission [26].



4. Saturated Fat

Diets lower in saturated fat have been associated with significantly greater reductions in LDL cholesterol and lower concentrations of large, buoyant LDL particles [34], whereas higher intakes of saturated fat have been associated with significantly greater increases in concentrations of small, dense LDL III particles, and higher contents of ApoC-III in LDL cholesterol particles, specifically LDL IV particles [36]. A 5% increase in saturated fat intake has been associated with a 36% greater risk of coronary heart disease in women in a 16-year follow-up study [37]. Similar findings assessing the risk of CVD-related events and death have been reported using data from the Nurse's Health Study [38]. Furthermore, substitution of carbohydrates and saturated fat with polyunsaturated fat has been associated with a decreased risk of coronary events and death [39]. Greater decreases in LDL cholesterol have been observed in individuals with lower levels of saturated fat intake [25,40]. Moreover, replacing saturated fatty acids with *cis* unsaturated fatty acids was found to decrease total:HDL cholesterol ratio, with *cis* monounsaturated fatty acids resulting in the greatest reduction in LDL cholesterol [41]. Despite accumulating findings that suggest a relationship between saturated fat intake and CVD risk, a meta-analysis of 21 prospective cohort studies with 5–23 years of follow-up found no significant association between saturated fat intake and risk of stroke or CVD when the data were pooled together, even though individual studies had reported significant associations [42]. Similarly, no significant differences in the number and frequency of cardiovascular events and deaths between diets differing in fat composition were reported following periods of over 2 years [43]. It, therefore, remains unclear whether saturated fats are more dangerous in promoting CVD compared to unsaturated fats. More research is needed to make accurate and appropriate dietary recommendations on which types of fats to consume and which to avoid to decrease overall CVD risk.

5. Protein Content

Dietary protein content also affects body weight and lipid profiles. While differences in dietary protein content appear to have similar effects on body weight, diets higher in protein may produce more favourable changes in lipid profiles. For example, replacing carbohydrates with protein was found to significantly reduce TG levels and LDL cholesterol [44]. Furthermore, a high-protein diet (48% of energy intake from carbohydrates, 27% from total fat—6% saturated, 13% monounsaturated, 8% polyunsaturated—and 25% from protein) led to greater decreases in ApoC-III content in LDL and VLDL cholesterol compared to low-fat (58% of energy intake from carbohydrates, 27% from total fat—6% saturated, 13% monounsaturated, 8% polyunsaturated—and 15% from protein) and unsaturated-fat (48% of energy intake from carbohydrates, 37% from total fat—6% unsaturated, 21% monounsaturated, and 10% polyunsaturated—and 15% from protein) diets, beneficial effects that appeared to be independent of those resulting from carbohydrate reduction alone [45]. Other studies have found contrasting results, whereby high-protein and high-carbohydrate diets with similar fat intake resulted in similar reductions in LDL and HDL cholesterol levels [46]. While these findings suggest the importance of substantial protein intake, other studies have reported that diets rich in protein may not sustain weight loss for long periods of time (≥3 months), and attribute the positive effects of high-protein diets on lipid profiles to weight loss. Furthermore, they may cause kidney and liver problems and increase risk of cardiovascular disease due to increased intake of saturated fatty acid and cholesterol associated with protein intake from animal sources [47].

The source of protein and fat can also impact whether the effects of a diet can be beneficial or not. For example, low-carbohydrate diets with protein and fat primarily from vegetable sources as opposed to animal sources were found to be associated with decreased CVD-related mortality and risk of CHD. In the Nurse's Health Study, vegetable fat intake was associated with a decreased risk of CHD, whereas no such association was found with animal fat intake [37]. Moreover, higher mortality rates in the Nurse's Health Study and the Health Professional's Follow-up Study have been associated with low-carbohydrate scores that had primarily animal sources of fat and protein [48].

6. Literature Shortcomings

One major difficulty with studies monitoring diets in large cohorts is the accuracy of self-reported measures, which are commonly used to monitor dietary intake over the course of the experiment. Studies have found that questionnaires such as the food-frequency questionnaires (FFQs), 24-hour recall, 4-day weighed food recalls and 7-day diaries, which are commonly used in cohort studies, led to inaccurate reports of dietary intake and consequently underestimations of relative risk calculations due to intake-related and person-related biases [49,50]. In contrast, other studies have reported close associations between actual dietary intake and that reported by the FFQs, although large individual differences were observed [51]. However, even though FFQs could provide somewhat accurate data in certain individuals, many studies lack repeated measures of dietary intake that could improve overall accuracy of these classifications [37]. Thus, discrepancies between studies may result from imprecision due to subjective assessment methods, ultimately leading to inconclusive findings on the long-term effects of various diets. While associations between diets and lipid profiles may be stronger in

shorter-term studies due to greater control over the participants' diets and higher compliance rates, they provide no insight as to these effects in the long-term. Furthermore, publication bias and the favouring of studies with positive results also lead to biased knowledge about the dietary effects on health. Such publication bias has been found in a number of cohort studies [20,40], while others have included unpublished cohort studies in an effort to reduce this effect [37].

7. Conclusion

The challenges that accompany scientific research in this area result in an inability to conclusively determine the most effective macronutrient compositions required for the reduction of CVD risk. Diets low in fat content generally reduce total, LDL, and HDL cholesterol, whereas diets low in carbohydrates reduce TG levels and VLDL cholesterol, and increase HDL as well as LDL cholesterol. However, low-carbohydrate diets shift the size of LDL particles from small, dense LDL III and IV particles, which are more atherogenic, to larger, more buoyant LDL I and small IDL particles, which appear to be less dangerous in promoting CVD. In contrast, while low-fat diets lower total LDL cholesterol, LDL particle size is shifted more towards small, dense atherogenic particles. These findings suggest that focusing on specific subclasses of LDL particles rather than total LDL cholesterol levels is more accurate in assessing overall CVD risk, and dietary recommendations should target lowering levels of these dangerous LDL particles. Moreover, concentrations of ApoB and ApoC-III in LDL and VLDL particles may be particularly effective tools for the assessment of CVD risk, as these apolipoproteins affect how cholesterol particles are metabolized in the circulatory system [52], and may mediate conversions between different LDL subfractions [53]. Therefore, developing better methods to track dietary intake in the long-term, and shifting the focus of assessments from total:HDL ratios and LDL cholesterol to TG-rich, ApoB- and ApoC-III-containing LDL and VLDL particles could lead to more precise and accurate findings in future research in this field.

Importantly, dietary recommendations should be tailored to the needs of the individual, based on which markers are elevated or decreased and present a risk of CVD development. Recent research suggests that the average individual affected by or at risk for developing CVD has changed over the years, whereby most patients with coronary problems are also affected by some form of insulin resistance [36]. Therefore, this insulin resistance needs to be taken into consideration when giving dietary recommendations. Since being overweight is one of the risk factors for CVD development, diets low in carbohydrate content with moderate levels of protein intake appear to be the most efficient in reducing body weight in the long term, and because no caloric restriction is needed in order to see results.

Acknowledgements

This work was supported by funds from Concordia University.

Author Contributions

All authors contributed to the writing of this manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

References

1. *Global Status Report on Noncommunicable Diseases 2010*; World Health Organization: Geneva, Switzerland, 2011.
2. Centers for Disease Control and Prevention. Heart Disease and Stroke Prevention: Addressing the Nation's Leading Killers. 2011. Available online: http://www.cdc.gov/chronicdisease/resources/publications/aag/pdf/2011/heart-disease-and-stroke-aag-2011.pdf (accessed on 13 January 2014).
3. Health Canada. Canada's Food Guide. 2011. Available online: http://www.hc-sc.gc.ca/fn-an/food-guide-aliment/index-eng.php (accessed on 28 November 2013).
4. The American Heart Association's Diet and Lifestyle Recommendations. Available online: http://www.heart.org/HEARTORG/GettingHealthy/Diet-and-Lifestyle-Recommendations_UCM_305855_Article.jsp (accessed on 20 November 2013).
5. Austin, M.A. Epidemiology of hypertriglyceridemia and cardiovascular disease. *Am. J. Cardiol.* **1999**, *83*, 13–16.
6. Hokanson, J.E.; Austin, M.A. Plasma triglyceride level is a risk factor for cardiovascular disease independent of high-density lipoprotein cholesterol level: A metaanalysis of population-based prospective studies. *Eur. J. Prev. Cardiol.* **1996**, *3*, 213–219.
7. Shankar, A.; Mitchell, P.; Rochtchina, E.; Wang, J.J. The association between circulating while blood cell count, triglyceride level and cardiovascular and all-cause mortality: Population-based cohort study. *Atherosclerosis* **2007**, *192*, 177–183.
8. Gould, A.L.; Davies, G.M.; Alemao, E.; Yin, D.D.; Cook, J.R. Cholesterol reduction yields clinical benefits: meta-analysis including recent trials. *Clin. Therapeut.* **2007**, *29*, 778–794.
9. Manninen, V.; Tenkanen, L.; Koskinen, P.; Huttunen, J.K.; Manttari, M.; Heinonen, O.P.; Frick, M.H. Joint effects of serum triglyceride and ldl cholesterol and hdl cholesterol concentrations on coronary heart disease risk in the Helsinki heart study. Implications for treatment. *Circulation* **1992**, *85*, 37–45.
10. Briel, M.; Ferreira-Gonzalez, I.; You, J.J.; Karanicolas, P.J.; Akl, E.A.; Wu, P.; Blechacz, B.; Bassler, D.; Wei, X.; Sharman, A.; *et al.* Association between change in high density lipoprotein cholesterol and cardiovascular disease morbidity and mortality: Systematic review and meta-regression analysis. *Brit. Med. J.* **2009**, *338*, doi:10.1136/bmj.b92.
11. Sacks, F.M.; Alaupovic, P.; Moye, L.A.; Cole, T.G.; Sussex, B.; Stampfer, M.J.; Pfeffer, M.A.; Braunwald, E. Vldl, Apolipoproteins v, cIII, and e, and risk of recurrent coronary events in the cholesterol and recurrent events (care) trial. *Circulation* **2000**, *102*, 1186–1892.
12. Van Gaal, L.F.; Wauters, M.A.; De Leeuw, I.H. The beneficial effects of modest weight loss on cardiovascular risk factors. *Int. J. Obes. Relat. Metab. Disorders* **1997**, *21*, S5–S9.

13. Hu, T.; Mills, K.T.; Yao, L.; Demanelis, K.; Eloustaz, M.; Yancy, W.S.; Kelly, T.N., Jr.; Bazzano, L.A.; *et al.* Effects of low-carbohydrate diets versus low-fat diets on metabolic risk factors: A meta-analysis of randomized controlled clinical trials. *Am. J. Epidemiol.* **2012**, *176*, S44–S54.
14. Sacks, F.M.; Bray, G.A.; Carey, V.J.; Smith, S.R.; Ryan, D.H.; Anton, S.D.; McManus, K.; Champagne, C.M.; Bishop, L.M.; Laranjo, N. Comparison of weight-loss diets with different compositions of fat, protein, and carbohydrates. *New England J. Med.* **2009**, *360*, 859–873.
15. Shai, I.; Schwarzfuchs, D.; Henkin, Y.; Shahar, D.R.; Witkow, S.; Greenberg, I.; Golan, R.; Fraser, D.; Bolotin, A.; Vardi, H.; *et al.* Weight loss with a low-carbohydrate, Mediterranean, or low-fat diet. *New England J. Med.* **2008**, *359*, 229–241.
16. Bueno, N.B.; Vieira de Melo, I.S.; Lima de Oliveira, S.L.; da Rocha Ataide, T. Very-low-carbohydrate ketogenic diet v. low-fat diet for long-term weight loss: A meta-analysis of randomised controlled trials. *Brit. J. Nutr.* **2013**, *110*, 1178–1187.
17. Krieger, J.W.; Sitren, H.S.; Daniels, M.J.; Langkamp-Henken, B. Effects of variation in protein and carbohydrate intake on body mass and composition during restriction: A meta-regression. *Am. J. Clin. Nutr.* **2006**, *83*, 260–274.
18. Volek, J.S.; Sharman, M.J.; Gómez, A.L.; DiPasquale, C.; Roti, M.; Pumerantz, A.; Kraemer, W.J. Comparison of a very low-carbohydrate and low-fat diet on fasting lipids, ldl subclasses, insulin resistance, and postprandial lipemic responses in overweight women. *J. Am. College Nutr.* **2004**, *23*, 177–184.
19. Howard, B.V.; Van Horn, L.; Hsia, J.; Manson, J.E.; Stefanick, M.L.; Wassertheil-Smoller, S.; Kotchen, J.M. Low-fat dietary pattern and risk of cardiovascular disease: The women's health initiative randomized controlled modification trial. *J. Am. Med. Assoc.* **2006**, *295*, 655–666.
20. Brehm, B.J.; Seeley, R.J.; Daniels, S.R.; D'Alessio, D.A. A randomized trial comparing a very low carbohydrate diet and a calorie-restricted low fat diet on body weight and cardiovascular risk factors in healthy women. *J. Clin. Endocrinol. Metab.* **2003**, *88*, 1617–1623.
21. Ruth, M.R.; Port, A.M.; Shah, M.; Bourland, A.C.; Istfan, N.W.; Nelson, K.P.; Gokce, N.; Apovian, C.M. Consuming a hypocaloric high fat low carbohydrate diet for 12 weeks lowers c-reactive protein, and raises serum adiponectin and high density lipoprotein-cholesterol in obese subjects. *Metabolism* **2013**, *62*, 1779–1787.
22. Schwingshackl, L.; Hoffmann, G. Comparison of effects of long-term low-fat *vs.* high-fat diets on blood lipid levels in overweight or obese patients: A systematic review and meta-analysis. *J. Acad. Nutr. Diet.* **2013**, *113*, 1640–1661.
23. Fung, T.T.; Chiuve, S.E.; McCullough, M.L.; Rexrode, K.M.; Logroscino, G.; Hu, F.B. Adherence to a dash-style diet and risk of coronary heart disease and stroke in women. *Arch. Inter. Med.* **2008**, *168*, 713–720.
24. Obarzanek, E.; Sacks, F.M.; Vollmer, W.M.; Bray, G.A.; Miller, E.R., III; Lin, P.-H.; Karanja, N.M.; Most-Windhauser, M.M.; Moore, T.J.; Swain, J.F.; Bales, C.W.; Proschan, M.A.; DASH Research Group. Effects on blood lipids of a blood pressure-lowering diet; the dietary approaches to stop hypertension (dash) trial. *Am. J. Clin. Nutr.* **2001**, *74*, 80–89.

25. Howard, B.V.; Curb, J.D.; Eaton, C.B.; Kooperberg, C.; Ockene, J.; Kostis, J.B.; Pettinger, M.; Rajkovic, A.; Robinson, J.G.; Rossouw, J.; Sarto, G.; Shikany, J.M.; Van Horn, L. Low-fat dietary pattern and lipoprotein risk factors: The women's health initiative dietary modification trial. *Am. J. Clin. Nutr.* **2010**, *91*, 860–874.
26. Dreon, D.M.; Fernstrom, H.A.; Williams, P.T.; Krauss, R.M. A very-low-fat diet is not associated with improved lipoprotein profiles in men with a predominance of large, low-density lipoproteins. *Am. J. Clin. Nutr.* **1999**, *69*, 411–418.
27. Gardner, C.D.; Kiazand, A.; Alhassan, S.; Stafford, R.S.; Balise, R.R.; Kraemer, H.C.; King, A.C. Comparison of the atkins, zone, ornish, and LEARN diets for change in weight and related risk factors among overweight premenopausal women. *J. Am. Med. Assoc.* **2007**, *297*, 969–976.
28. Austin, M.A.; Breslow, J.L.; Hennekens, C.H.; Buring, J.E.; Willet, W.C.; Krauss, R.M. Low-density lipoprotein subclass patterns and risk of myocardial infarction. *J. Am. Med. Assoc.* **1988**, *260*, 1917–1921.
29. Austin, M.A.; King, M.C.; Vranizan, K.M.; Krauss, R.M. Atherogenic lipoprotein phenotype. A proposed genetic marker for coronary heart disease risk. *Circulation* **1990**, *82*, 495–506.
30. Williams, P.T.; Krauss, R.M. Associations of age, adiposity, menopause, and alcohol intake with low-density lipoprotein subclasses. *Arterioscl. Thromb. Vascul. Biol.* **1997**, *17*, 1082–1090.
31. Dreon, D.M.; Fernstrom, H.A.; Miller, B.; Krauss, R.M. Low-density lipoprotein subclass patterns and lipoprotein response to a reduced-fat diet in men. *J. Fed. Am. Soc. Exper. Biol.* **1994**, *8*, 121–126.
32. Carmena, R.; Duriez, P.; Fruchart, J.-C. Atherogenic lipoprotein particles in atherosclerosis. *Circulation* **2004**, *109* (23 Suppl 1), III2–III7.
33. Lee, S.-J.; Campos, H.; Moye, L.A.; Sacks, F.M. Ldl containing Apolipoprotein cIII is an independent risk factor for coronary events in diabetic patients. *Atheroscl. Thromb. Vascul. Biol.* **2003**, *23*, 853–858.
34. Krauss, R.M.; Blanche, P.J.; Rawlings, R.S.; Fernstrom, H.S.; Williams, P.T. Separate effects of reduced carbohydrate intake and weight loss on atherogenic dyslipidemia. *Am. J. Clin. Nutr.* **2006**, *83*, 1025–1031.
35. Faghihnia, N.; Mangravite, L.M.; Chiu, S.; Bergeron, N.; Krauss, R.M. Effects of dietary saturated fat on ldl subclasses and Apolipoprotein cIII in men. *Eur. J. Clin. Nutr.* **2012**, *66*, 1229–1233.
36. Scholl, J. Traditional dietary recommendations for the prevention of cardiovascular disease: Do they meet the needs of our patients? *Cholesterol* **2012**, doi:10.1155/2012/367898.
37. Jakobsen, M.U.; Overvad, K.; Dyerberg, J.; Schroll, M.; Heitmann, B.L. Dietary fat and risk of coronary heart disease: Possible effect modification by gender and age. *Am. J. Epidemiol.* **2004**, *160*, 141–149.
38. Hu, F.B.; Stampfer, M.J.; Manson, J.E.; Rimm, E.; Colditz, G.A.; Rosner, B.A.; Willett, W.C. Dietary fat intake and the risk of coronary heart disease in women. *New England J. Med.* **1997**, *337*, 1491–1499.
39. Jakobsen, M.U.; O'Reilly, E.J.; Heitmann, B.L.; Pereira, M.A.; Bälter, K.; Fraser, G.E.; Ascherio, A. Major types of dietary fat and risk of coronary heart disease: A pooled analysis of 11 cohort studies. *Am. J. Clin. Nutr.* **2009**, *89*, 1425–1432.

40. Cuchel, M.; Schwab, U.S.; Jones, J.H.; Vogel, S.; Lammi-Keefe, C.; Li, Z.; Lichtenstein, A.H. Impact of hydrogenated fat consumption on endogenous cholesterol synthesis of low-density lipoprotein to oxidation in moderately hypercholesterolemic individuals. *Metabolism* **1996**, *45*, 241–247.
41. Mensink, R.P.; Zock, P.L.; Kester, A.D.M.; Katan, M.B. Effects of dietary fatty acids and carbohydrates on the ratio of serum total to hdl cholesterol and on serum lipids and Apolipoproteins: A meta-analysis of 60 controlled trials. *Am. J. Clin. Nutr.* **2003**, *77*, 1146–1155.
42. Siri-Tarino, P.W.; Sun, Q.; Hu, F.B.; Krauss, R.M. Meta-analysis of prospective cohort studies evaluating the association of saturated fat with cardiovascular disease. *Am. J. Clin. Nutr.* **2010**, *91*, 535–546.
43. Frantz, I.D.; Dawson, E.A., Jr.; Ashman, P.L.; Gatewood, L.C.; Bartsch, G.E.; Kuba, K.; Brewer, E.R. Test of effect of lipid lowering by diet on cardiovascular risk. The Minnesota coronary survey. *Arterioscl. Thromb. Vascul. Biol.* **1989**, *9*, 129–135.
44. Appel, L.J.; Sacks, F.M.; Obarzanek, E.; Swain, J.F.; Miller, E.R.; Conlin, P.R.; Erlinger, T.P.; Rosner, B.A.; Laranjo, N.M.; Charleston, J.; McCarron, P. Bishop, L.M.; OmniHeart Collaborative Research Group. Effects of protein, monounsaturated fat, and carbohydrate intake on blood pressure and serum lipids: Results of the omniheart randomized trial. *J. Am. Med. Assoc.* **2005**, *294*, 2455–2464.
45. Furtado, J.D.; Campos, H.; Appel, L.J.; Miller, E.R.; Laranjo, N.; Carey, V.J.; Sacks, F.M. Effect of protein, unsaturated fat, and carbohydrate intakes on plasma Apolipoprotein b and vldl and ldl containing Apolipoprotein c-III: Results from the omniheart trial. *Am. J. Clin. Nutr.* **2008**, *87*, 1623–1630.
46. Noakes, M.; Keogh, J.B.; Foster, P.R.; Clifton, P.M. Effect of an energy-restricted, high-protein, low-fat diet relative to a conventional high-carbohydrate, low-fat diet on weight loss, body composition, nutritional status, and markers of cardiovascular health in obese women. *Am. J. Clin. Nutr.* **2005**, *81*, 1298–1306.
47. St Sachiko, T.J.; Howard, B.V.; Prewitt, E.; Bovee, V.; Bazzarre, T.; Eckel, R.H.; Nutrition Committee of the Council on Nutrition, Physical Activity, and Metabolism of the American Heart Association. Dietary protein and weight reduction: A statement for healthcare professionals from the nutrition committee of the council on nutrition, physical activity, and metabolism of the American heart association. *Circulation* **2001**, *104*, 1869–1874.
48. Fung, T.T.; van Dam, R.M.; Hankinson, S.E.; Willett, W.C. Low-carbohydrate diets and all-cause and cause-specific mortality: Two cohort studies. *Ann. Inter. Med.* **2010**, *153*, 289–298.
49. Kipnis, V.; Midthune, D.; Freedman, L.; Bingham, S.; Day, N.E.; Riboli, E.; Ferrari, P.; Carroll, R.J. Part E. New statistical approaches to dealing with bias associated with dietary data: Bias in dietary-report instruments and its implications for nutritional epidemiology. *Public Health Nutr.* **2002**, *5*, 915–923.
50. Kipnis, V.; Subar, A.F.; Midthune, D.; Freedman, L.S.; Ballard-Barbash, R.; Troiano, R.P.; Carroll, R.J. Structure of dietary measurement error: Results of the open biomarker study. *Am. J. Epidemiol.* **2003**, *158*, 14–21.
51. Siebelink, E.; Geelen, A.; de Vries, J.H.M. Self-reported energy intake by FFQ compared with actual energy intake to maintain body weight in 516 adults. *Brit. J. Nutr.* **2011**, *106*, 274–281.

52. Zheng, C.; Khoo, C.; Ikewaki, K.; Sacks, F.M. Rapid turnover of Apolipoprotein C-III-containing triglyceride-rich lipoproteins contributing to the formation of ldl subfractions. *J. Lipid Res.* **2007**, *48*, 1190–1203.
53. Campos, H.; Dreon, D.M.; Krauss, R.M. Associations of hepatic and lipoprotein lipase activities with changes in dietary composition and low density lipoprotein subclasses. *J. Lipid Res.* **1995**, *36*, 462–472.