# Research Article

## Intermittent fasting and low-carbohydrate diet to improve cardiovascular risk factor in obese adolescent

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**Abstract**:

**Background**: The prevalence of obesity in children and adolescents are increasing during recent years. Youth obesity is a risk for obesity in adulthood and associated with the development of cardiovascular risk factors. Increasing inflammation and oxidative stress in obesity have principal roles in the pathogenesis of the chronic disease. Fasting and low-carbohydrate high-fat (LCHF) diet are known to have therapeutic roles besides weight loss.

**Aims**: To review relevant studies related to intermittent fasting and low-carbohydrate diets and their correlation to cardiovascular disease in the obese adolescent.

**Review Result**: The nutritional ketosis state enables the use of ketone as the primary energy source. The shifting metabolism to ketone can enhance insulin sensitivity and ameliorate the inflammation progress which resulted in improvement of metabolic syndrome features and oxidative stress biomarker. Weight loss occurred as a result of increasing lipolysis and hunger suppression effect of the ketone. Several common concerns related to carbohydrate restriction are carbohydrate as essential nutrition, risk of high free fat intake, and ketone toxicity. The potential side effect in the regulation of electrolytes is yet to be clinically proven.

**Conclusion**: Ketosis nutritional benefits not limited to only weight loss, but also in the overall improvement of cardiovascular disease risk factors.

**Keywords**: Obesity, fasting, low-carbohydrate high-fat diet, cardiovascular risk

**Introduction**

Obesity in childhood is defined as a BMI at or above the 95th percentile for children and teens of the same age and sex.[1] Globally, around one in 10 young people aged 5-17 years are overweight or obese, with levels increasing rapidly in recent years. Prevention of obesity in childhood is needed to ensure healthy lives and promote well-being for all at all ages, which was addressed in the Sustainable Development Goals by reducing one-third of premature mortality from non-communicable diseases by 2030. In Indonesia, the most recent reported prevalence of overweight in children under five is 8%.[2]

The primary cause of obesity is the obesogenic environment as the key driver for low physical activity and increase intake of high-calorie food.[3] The shift in macronutrient from fat to carbohydrate contributed as well to the increasing obesity. In a statistical review of US macronutrient consumption, from 1965 to 2011 the percentage of overweight or obese Americans has increased from 42% to 66% with a corresponding rise in absolute consumption of carbohydrate from 39% to 51% of total caloric intake.[4] A cross-sectional study in Indonesia performed on 92 obese adolescents in 2013 found that dyslipidemia in obesity was in 4,3% of subjects.[5]

Overweight adolescents have a 40-80% chance of becoming overweight or obese adults.[6] Inflammation and oxidative stress in obesity play as the main role in causing insulin resistance (IR) and atherosclerosis.[7] Metabolic syndrome, a cluster of cardio-metabolic risk factors, have been identified in obese children.[8] Level of c-reactive protein (CRP) and malondialdehyde (MDA), the early markers of cardiovascular disease (CVD), increased significantly in pre-pubertal children aged 6-10 years with extreme obesity (higher than 99th percentile) compared to obese and overweight subjects. [9,10,11]

Fasting and diet, a modification in caloric intake, are means to overcome childhood obesity. Fasting is intermittent elimination of caloric intake meanwhile, diet is a modification of type and nutrient composition with or without caloric restriction.[12,13] Ketogenic diet, the most frequently studied type of diet, is a restriction in daily intake of carbohydrate (below 50 g/day) with high fat and moderate protein intake without caloric restriction.[14,15] In the state of low carbohydrate intake, keto-adaptation will occur and shift the metabolism fuel to correct metabolic syndrome.

This article aims to review the relevant studies related to intermittent fasting and low-carbohydrate diet and their correlation to CVD in an obese adolescent.

**Obesity**

The prevalence of childhood and adolescent obesity has increased more than ten-fold in the last four decades, from 11 million in 1975 to 124 million populations in 2016. 73% of the increase was due to an increase in the prevalence of obesity meanwhile, the rest was affected by population growth.[16] The conventional theory on obesity causes is a simple thermodynamic hypothesis. This physical law said that obesity results from a net positive energy balance or the ingestion of caloric greater than that required by the body thus, leading to accumulation of fat.[17]

The alternative theory on obesity causes is the endocrinological hypothesis or hormonal regulation disorder. Insulin, an anabolic hormone in glucose homeostasis, is a primary regulator of lipid accumulation. [17] IR occurs when the insulin-sensitive tissue loss response to insulin.[7] Selective IR still enables de-novo lipogenesis despite the resistance in glucose handling, which resulting in fat

accumulation and obesity.[18] Moreover, the increase in adipose tissue results in inflammation and oxidative stress and aggravate IR.[19]

Pulungan et al. reported the prevalence of IR in obese adolescents in Jakarta, Indonesia is 38%, using the homeostasis model assessment for IR (HOMA-IR) measurement method. The study revealed that IR in obese adolescents was highest among girls, individuals with a family history of obesity, and individuals with symptoms of acanthosis nigricans. Less than 10% of obese adolescents had impaired fasting glucose, but no obese teenagers with type-2 diabetes mellitus were present.[20] Several theories have connected the link between the incidence of obesity, metabolic syndrome, and IR. Obesity can result in IR and endothelial dysfunction through a series of reciprocal metabolism of fat, hormones, and adipocytokines.[20]

Obesity-associated inflammation is an underlying key of the pathophysiologic process in the development of chronic disease including type 2 diabetes, hypertension, atherosclerosis, fatty liver and certain types of cancer.[7] Inflammation is characterized by elevated macrophage infiltration to adipose tissue and liver and increased levels of pro-inflammatory cytokines like CRP, interleukin 6 (IL-6), and plasminogen activator inhibitor-1 (PAI-1). Overreaction of inflammatory response lead to tissue injury and organ dysfunction. Inflammation inhibits insulin signaling activity through the inhibition of insulin receptor substrate-1 (IRS-1) in adipocytes and hepatocytes. IR also related to mitochondrial dysfunction, a reduction in mitochondrial number, density or function. Mitochondrial dysfunction may contribute to the accumulation of free fatty acid and fat in favor of IR.[7]

**Obesity and cardiovascular risk factor**

One of the important health implication of childhood obesity includes the development of CVD risk factor.[6] One population-based study estimated that 70% of children between the ages of 5-17 have at least one cardiovascular risk factor.[21] A concept frequently used in characterizing the relationship between childhood obesity and the risk of chronic disease is metabolic syndrome (Table 1).[8] More than 40 definitions for childhood metabolic syndrome have been proposed, most are the adaptation of adult criteria.[22] Despite their differences, the common features are obesity (BMI or waist circumference), high blood pressure, impaired glucose tolerance (fasting glucose or insulin level) and poor lipid profile (triglyceride, low-density lipoprotein (LDL) and high-density lipoprotein (HDL)).[8] LDL consists of several particle subclasses with different density including large buoyant (lb-LDL) and small dense (sd-LDL). The sd-LDL has a more potent atherogenic feature and is a better predictor for CVD.

| Criteria | Value |
|---|---|
| Obesity (waist circumference) | Greater than or equal to the 90$^{th}$ percentile or adult cut off if lower |
| Triglyceride | ≥150mg/dL |
| HDL-C | < 40 mg/dL |
| Blood pressure | Systolic above 130 mmHg or diastolic above 85 mmHg |
| Glucose | ≥100 mg/dL or known type 2 diabetes |

**Table 1.** Diagnostic criteria of metabolic syndrome in children ages 10-16[23]

Other biochemical parameters to predict cardiovascular risk in obesity are inflammation markers such as CRP and MDA. Serum CRP is mainly synthesized in the liver and its levels are elevated in response to inflammatory conditions. The high sensitivity CRP (hs-CRP) assay helps to quantify low grades of

systemic inflammation. The hs-CRP is the most widely evaluated biomarker for cardiovascular risk prediction.[9] MDA is the secondary byproduct of lipid peroxidation, a reaction of reactive oxygen species with lipids.[10] Higher concentrations of MDA has been observed in children with obesity compared to normal weight and reflected the oxidative stress level.[19]

Ultrasound carotid intima-media thickness (CIMT) is a non-invasive technique used for the assessment of subclinical CVD and as a surrogate for treatment efficacy in the clinical setting.[24] Increased CIMT is an adaptive response to the known atherosclerosis-related pathophysiology like a change in blood flow and increased intraluminal pressure.[25] Substantial weight loss associated with a decrease in CIMT in children with obesity. The previous study found a decrease in CIMT (0.07mm) consistent with significant BMI reduction (mean 2.2 kg/$m^2$).[26]

The intervention to childhood obesity consists of adjustment in dietary habit, physical activity and behavior modification with parents as the role models.[27] The intervention should be adjusted according to age and developmental stage in children. The first step is to raise motivation in children and together make the deal regarding the target without forcing the children. Adjustment in dietary habits should follow the requirement of daily allowances with food rules, stick-to-meal, and snack frequency. Daily physical activity affects the appetite and increases metabolism rate. The physical activity can be an aerobic activity, muscle or bone strengthening on a daily basis for about 60 minutes. Parental support and appreciation are also a main component of behavior modification, such as self-control to limit daily intake. The more intensive interventions are pharmacotherapy to suppress appetite and bariatric surgery.[27]

**Fasting as an intervention to overcome obesity**

Fasting is one of the interventions to achieve weight loss in obese adolescents. Fasting is defined as no ingestion or minimal amount of food and caloric beverages for certain periods, typically range from 12 hours to 3 weeks.[12] Fasting is distinct from caloric restriction, in which daily caloric intake reduced chronically by 20-40% with maintained meal frequency. Meanwhile, starvation is an extreme form of fasting which can result in degeneration and death. Common different types of fasting are time-restricted feeding and intermittent fasting. Time-restricted feeding is limiting daily intake to 4 hours to 6 hours' time window.[28] Meanwhile, intermittent fasting is a short period fasting which includes alternate day fasting.[12]

Limitation in certain types of nutrients with or without caloric restriction is another optional method used to overcome obesity in the adolescent. Recently, ketogenic or low-carbohydrate diet is one type of diet which most frequently studied. The ketogenic diet is reducing carbohydrates intake and will relatively increasing the proportions of fat and/or protein without caloric restriction. [14,15] Each individual has a different limit of minimal carbohydrate intake to initiate ketosis and lipolysis (between 65-180 gram/day).[14] Ketogenic diet is not a high protein diet since protein is a potent trigger of insulin secretion thus, increasing the risk of IR.[29]

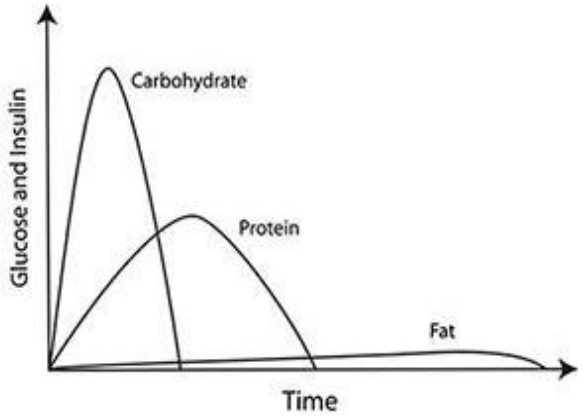


**Figure 1. Glucose and insulin response to macronutrients**[30]

Figure 1 shows that carbohydrate causes a significant spike in blood glucose and insulin level. The level then declines in a short period causing the body craves for another carbohydrate intake. Meanwhile, proteins cause considerably less, and fats cause almost no significant rise in blood glucose and insulin level. Their level decline in relatively longer periods which result in longer satiety. Thus, the conclusion is the elevated proportion of fat intake in a ketogenic diet does not cause in weight gain.[30]

**Shifting metabolism in fasting and a ketogenic diet**

The human starve-feed cycle composes of four global nutritional states:1) well-fed, 2) early fasting, 3) prolonged fasting or starvation 4) early re-fed. Of these four states, the most relevant model for a low carbohydrate diet is the metabolism of prolonged fasting.[14] During prolonged fasting state, the low carbohydrate intake will generate ketone bodies from free fatty acid, mainly occur in the mitochondrial matrix of liver tissues. Ketone then exits the liver to provide energy to all cells with mitochondria. Within a cell, ketone is converted for a generation of adenosine triphosphate (ATP).[15]

The term of ketone bodies refers to three metabolisms: acetoacetate, beta-hydroxybutyrate (b-OHB), and acetone. Acetoacetate mainly converted to the other two ketone bodies and acetone is primarily an excretory product. Therefore, b-OHB serves as transportable forms of energy (Figure 2).[14] The shifting metabolism in ketosis nutritional state initiated when the blood ketone level reaches 0.5 millimolar (mM).

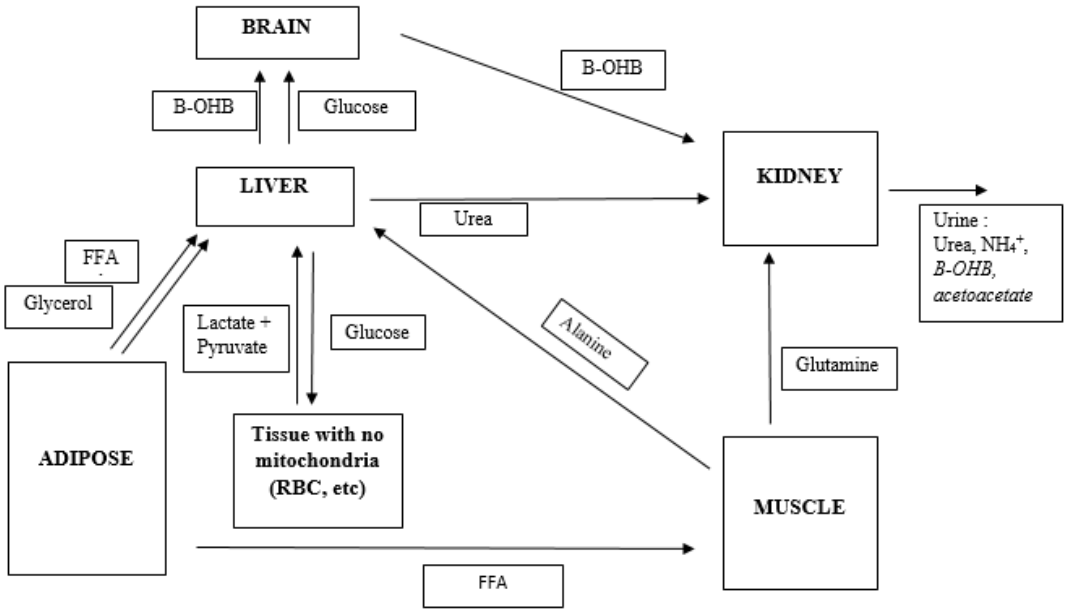


**Figure 2. The overall scheme of starvation fuel metabolism. The liver derives its major energy by partial oxidation of free fatty acid (FFA) to beta-hydroxybutyrate (b-OHB); muscle and kidney by complete oxidation of FFA to $CO_2$ and $H_2O$. The brain utilizes both b-OHB and glucose.[31](RBC: red blood cells)**

Blood glucose levels are sustained by breakdown muscle and liver glycogen and de novo gluconeogenesis from amino acids, glycerol, and lactate. Glycerol released from lipolysis of triglyceride in the adipocyte. This compensatory gluconeogenic mechanism is important to sustain glucose-dependent tissue like erythrocyte, cornea, and retina.[15] A combination of increased lipolysis and increased lipogenesis resulted in weight reduction. Moreover, modification in levels of appetite-related hormone (ghrelin and leptin) and neurotransmitter gamma-aminobutyric acid (GABA) result in the appetite-suppressant effect of ketosis.[32]

Ketosis condition in low-carbohydrate intake also results in the improvement of metabolic syndrome. Low-carbohydrate intake leads to a reduction in cellular glucose uptake and enhancement of fat oxidation, in which improve IR.[14] In a short term randomized controlled trial (RCT), ketogenic diet significantly reduced fasting insulin and HOMA-IR with a greater result compared to hypocaloric diet within six-months follow-up period.[33]

The ketogenic effect is not only in lowering blood triglyceride but also shows a positive effect on total cholesterol reduction and increases in HDL. Reduced blood insulin level leads to less activation of 3-hydroxy-3-methylglutaryl-CoA reductase, a key enzyme in cholesterol biosynthesis. This is likely to be the mechanism via which nutritional ketosis can improve lipid profiles.[15] Furthermore, the ketogenic diet has been reported to increase the size and volume of LDL particles. During two years follow up HDL level increase approximately 23% with low carbohydrate diet.[34]

Overall, carbohydrate restriction is still the most effective intervention to improve all features of metabolic syndrome. (Figure 3).[35–37]

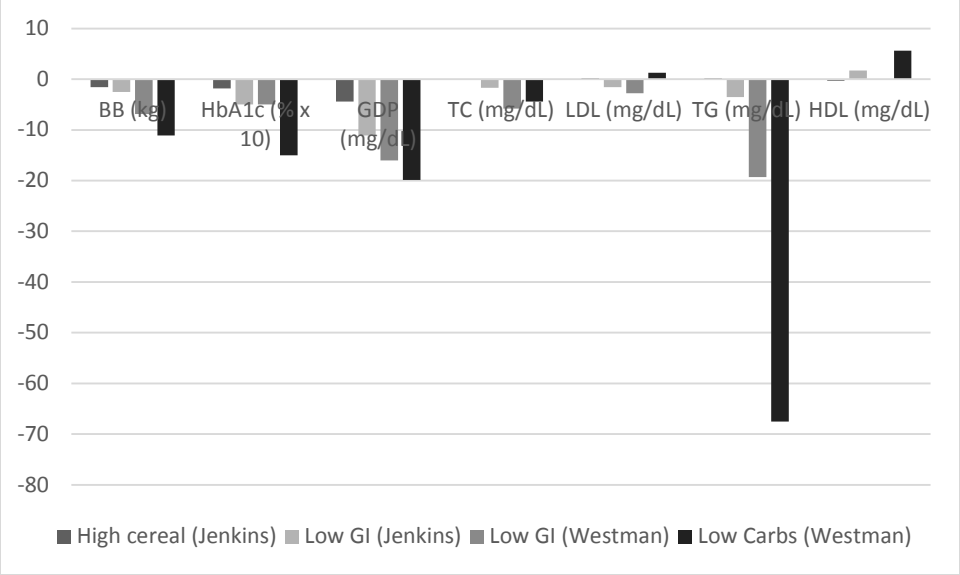


**Figure 3. Two similar studies compared high cereal diet, low glycemic index diet, and low-carbohydrate diet. The findings showed better improvement in low carbohydrate diet.[35–37] (BW: body weight, FG: fasting glucose, HDL: high-density lipoprotein, LDL: low-density lipoprotein, TG: triglyceride, TC: total cholesterol, GI: glycemic index)**

The decrease in CVD risk in the ketogenic diet has been associated with weight loss and reduced obesity-associated inflammation. In an RCT comparing high fat-low carbohydrate to a low-fat diet showed that low carbohydrate diet group had greater improvement in blood lipids and systemic inflammation despite the similar changes in body weight and composition.[38]

**Common concerns related to fasting and the ketogenic diet**

Several issues were commonly asked related to carbohydrate restricted diets. The first perspective is that carbohydrate is essential nutrition for balanced nutrition. In low carbohydrate intake, the glucose needs to be fulfilled by gluconeogenesis from amino acids, glycerol, and lactate, even while exercise. Nutritional science defines nine amino acids and two fatty acids (omega-3 and omega-6) as essentials,[39] and carbohydrate is not included. Therefore, in low carbohydrate intake, fat and amino acids can substitute the needs of glucose.

The second common perspective is the risk of high-fat intake. In the ketogenic diet, daily intake consists of fat up to 80% for total caloric. However, ketosis state causing an increase in fat oxidation and lipolysis to form energy. Lipid profiles are all improved in the ketogenic diet. The decrease in triglyceride levels occurred before significant weight loss.[14] The serum LDL level might be increased in the early phase of the diet, but it is well-established that not all LDL particles correlate with the risk of atherosclerosis. With the decrease in the ratio triglyceride to HDL showed an lb-LDL predominance.

Another perspective is the toxic effect of the ketone. Low carbohydrate intake indeed increased ketone production as a result of accelerated fat breakdown, though, ketone level in the nutritional ketosis stage is far below the pathological ketosis in uncontrolled diabetic ketoacidosis (Table 2). In physiological ketosis, maximum ketonemia at ketone level 7/8 mM/L. The use of ketone as energy fuel and the control mechanism by insulin prevents the abnormal increase of ketone.[40] In contrast, the blood ketone level in ketoacidosis can reach more than 25 mm/L with the change in blood pH.

| Serum level | Normal diet | Ketogenic diet | Diabetic ketoacidosis |
|---|---|---|---|
| Glucose (mg/dl) | 80-120 | 65-80 | >300 |
| Insulin (µU/L) | 6-23 | 6.6-9.4 | ~0 |
| Ketone (mM/L) | 0.1 | 7/8 | >25 |
| pH | 7.4 | 7.4 | <7.3 |

**Table 2. Comparison of blood levels during a normal diet, ketogenic diet, and diabetic ketoacidosis.**[15]

**Potential adverse effects**

Adverse effects that may occur including kidney stones formation and electrolyte imbalance. Yet, this effect has to be further monitored in clinical trials. [14] This effect related to the lower insulin level which decreases sodium reabsorption in the proximal tubule and inducing salt and water excretion.[39] The salt deprivation leads to lightheadedness, fatigue, headache, and malaise. The addition of extra sodium to daily intake can prevent the salt deprivation effects. Enough hydration and potassium citrate supplementation are a strategy to reduce the likelihood of kidney stones formation. In a study with an healthy obese subject, low-carbohydrate high-protein diet with a mean two years follow up, there was no decrease in glomerular filtration rate, albuminuria nor electrolyte imbalance.[41]

Bone demineralization related to relative acidosis conditions in the ketogenic diet has been reported to cause the increased prevalence of kidney stones.[42] Bone phosphate seems to act as an acid buffer, though, in an RCT comparing low fat and low carbohydrate diet outcome after two years, both showed no difference in bone mineral density change from baseline.[34] The supplementation of potassium citrate suggested the potential benefit to prevent kidney stones formation. Potassium citrate able to solubilize free calcium in the urine and increase urine pH to dissolve uric acid. [42]

**Conclusion**

Childhood and adolescent obesity are a risk factor for obesity in adulthood. Obesity is related to increased inflammation and oxidative stress of which causing insulin resistance, the key pathogenesis for metabolic syndrome and cardiovascular disease. The benefit from nutritional ketosis state in fasting and low-carbohydrate diet not limited to only weight loss, but for overall improvement in cardiovascular disease risk. Several adverse effects are rarely reported and can be prevented.

**References**

1. CDC National Center for Health Statistics. Percentile Data Files with LMS Values. 2000. http://www.cdc.gov/ nchs/data/nhanes/growthcharts/bmiage.txt. Accessed January 22, 2019.

2. Kementerian Kesehatan Republik Indonesia. Hasil Utama Riskesdas 2018. 2018:1-61.

3. WHO. Adolescent obesity and related behaviours: trends and inequalities in the WHO European region 2002-2014. *WHO Reg Publ Eur Ser*. 2017:2002-2014.

4. Cohen E, Cragg M, DeFonseka J, Hite A, Rosenberg M, Zhou B. Statistical review of US macronutrient consumption data, 1965-2011: Americans have been following dietary guidelines, coincident with the rise in obesity. *Nutrition*. 2015;31:727-732.

5. Pulungan AB, Puspitadewi A, Sekartini R. Prevalence of insulin resistance in obese adolescents. *Paediatr Indones*. 2013;53:167-172.

6. Umer A, Kelley GA, Cottrell LE, Giacobbi P, Innes KE, Lilly CL. Childhood obesity and adult cardiovascular disease risk factors: A systematic review with meta-analysis. *BMC Public Health*. 2017;17:1-24.

7. Ye J. Mechanisms of insulin resistance in obesity. *Front Med*. 2013;7:14-24.

8. Nehus E, Mitsnefes M. Childhood obesity and the metabolic syndrome. *Pediatr Clin North Am*. 2019;66:31-43.

9. Kamath DY, Xavier D, Sigamani A, Pais P. High sensitivity C-reactive protein (hsCRP) & cardiovascular disease: An Indian perspective. *Indian J Med Res*. 2015;142:261-268.

10. Ayala A, Munoz MF, Arguelles S. Lipid peroxidation: production, metabolism, and signaling mechanisms of malondialdehyde and 4-hydroxy-2-nonenal. *Oxid Med Cell Longev*. 2014:9-12.

11. Sidiartha IGL, Pertiwi NLPSC. Comparison of inflammation and oxidative stress levels by the severity of obesity in prepubertal children. *Paediatr Indones*. 2017;57:279-284.

12. Longo VD, Mattson MP. Review fasting : molecular mechanisms and clinical applications. *Cell Metab*. 2014;19(2):181-192.

13. Weickert MO. Nutritional modulation of insulin resistance. *Scientifica (Cairo)*. 2012:1-15.

14. Westman EC, Mavropoulos J, Yancy WS, Volek JS. A review of low-carbohydrate ketogenic diets. *Curr Atheroscler Rep*. 2003;5:476-483.

15. Paoli A, Rubini A, Volek JS, Grimaldi KA. Beyond weight loss : a review of the therapeutic uses of very-low-carbohydrate (ketogenic) diets. *Eur J Clin Nutr*. 2013;67(8):789-796.

16. NCD Risk Factor Collaboration. Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128.9 million children, adolescents, and adults. *Lancet*. 2017;390:2627-2642.

17. Taubes G. The science of obesity: what do we really know about what makes us fat ? An essay by Gary Taubes. *BMJ*. 2013;1050:1-5.

18. Williams KJ, Wu X. Imbalanced insulin action in chronic overnutrition: clinical harm, molecular mechanisms, and a way forward. *Atherosclerosis*. 2016;247:225-282.

19. AS M, HS T, CF N, et al. Oxidative stress and biochemical parameters in childhood obesity. *Austin J Nutr Food Sci*. 2018;1:1-5.

20. Pulungan AB, Afifa TI, Annisa D. Type 2 diabetes mellitus in children and adolescent: an Indonesian perspective. *Ann Pediatr Endocrinol Metab*. 2018;23:119-125.

21. Freedman DS, Mei Z, Srinivasan SR, Berenson GS, Dietz WH. Cardiovascular risk factors and excess adiposity among overweight children and adolescents: the Bogalusa heart study. *J Pediatr*. 2007;150:12-17.

22. Ford ES, Li C. Defining the metabolic syndrome in children and adolescents: Will the real definition please stand up? *J Pediatr*. 2008;152:160-164.

23. International Diabetes Federation. The IDF consensus definition of the metabolic syndrome in children and adolescent. *IDF*. 2007.

24. Epure AM, Leyvraz M, Mivelaz Y, et al. Risk factors and determinants of carotid intima-media thickness in children: Protocol for a systematic review and meta-analysis. *BMJ Open*. 2018;8.

25. Kwak BR, Bäck M, Bochaton-Piallat ML, et al. Biomechanical factors in atherosclerosis: Mechanisms and clinical implications. *Eur Hear J*. 2014;35:3013-3020.

26. Wunsch R, de Sousa G, Toschke AM, Reinehr T. Intima-media thickness in obese children before and after weight loss. *Pediatrics*. 2006;118:2334-2340.

27. Ikatan Dokter Anak Indonesia. Rekomendasi Ikatan Dokter Anak Indonesia Diagnosis, Tata Laksana dan Pencegahan Obesitas pada Anak dan Remaja. 2014.

28. Mattson MP, Allison DB, Fontana L, et al. Meal frequency and timing in health and disease. *Proc Natl Acad Sci U S A*. 2014;111:16647-16653.

29. Wilcox G. Insulin and Insulin Resistance. *Clin Biochem Rev*. 2005;26:19-39.

30. Thompson C. Reversing Diabetes, Insulin Resistance, and Obesity – What's the Chance? 2016. http://www.wholife.com/issues/21_6/03_article.html. Accessed February 7, 2019.

31. Cahill GF. Fuel metabolism in starvation. *Annu Rev Nutr*. 2006;26:1-22.

32. Paoli A, Bosco G, Camporesi EM, Mangar D. Ketosis, ketogenic diet and food intake control: a complex relationship. *Front Psychol*. 2015;6:1-9. doi:10.

33. Partsalaki I, Karvela A, Spiliotis BE. Metabolic impact of a ketogenic diet compared to a hypocaloric diet in obese children and adolescents. *J Pediatr Endocr Met*. 2012;25:697-704.

34. Foster GD, Wyatt HR, Hill JO, et al. Weight and metabolic outcomes after 2 years on a low-carbohydrate versus low-fat diet. *Ann Intern Med*. 2010;153:147-157.

35. Feinman RD, Ph D, Pogozelski WK, et al. Dietary carbohydrate restriction as the first approach in diabetes management : Critical review and evidence base. *Nutrition*. 2015;31:1-13.

36. Westman EC, Jr WSY, Mavropoulos JC, Marquart M, Mcduffie JR. The effect of a low-carbohydrate, ketogenic diet versus a low-glycemic index diet on glycemic control in type 2 diabetes mellitus. *Nutr Metab*. 2008;9:1-9.

37. Jenkins DJA, Kendall CWC, Mckeown-eyssen G, et al. Effect of a Low – Glycemic Index or a High – Cereal Fiber Diet on Type 2 Diabetes. *JAMA*. 2008;300:2742-2753.

38. Ruth MR, Port AM, Shah M, et al. 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*. 2013:6-14.

39. Volek JS, Phinney SD. *The Art and Science of Low Carbohydrate Living: An Expert Guide to Making the Life-Saving Benefits of Carbohydrate Restriction Sustainable and Enjoyable*. Beyond Obesity; 2011.

40. Grabacka M, Pierzchalska M, Dean M, Reiss K. Regulation of ketone body metabolism and the role of PPAR α. *Int J Mol Sci*. 2016;17:1-24.

41. Friedman AN, Ogden LG, Foster GD, et al. Comparative effects of low-carbohydrate high-protein versus low-fat diets on the kidney. *Clin J Am Soc Nephrol*. 2012;7:1103-1111.

42. Sampath A, Kossoff EH, Furth SL, Pyzik PL, Vining EPG. Kidney stones and the ketogenic diet: risk factors and prevention. *J Child Neurol*. 2007;22:375-378.