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Effect of Variant Carbohydrate Dietary on Cardiovascular Diseases

Review Research

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SUPERVISOR CERTIFICATION

I certify that this review research entitled with (**Effect of Variant Carbohydrate Dietary on Cardiovascular Diseases**) was done under my supervision by the undergraduate students by (**Nada Thair Khudhair**) at the college of Medicine – University of Diyala as partial fulfillment of the requirement for the B. Sc. In general medicine and surgery degree in academic year 2020-2021.



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Abstract

Background: The carbohydrate-to-fiber ratio is a recommended measure of carbohydrate quality; however, its relation to incident coronary heart disease (CHD) is currently well known but, the fast changes of the life styles done some modification in relation between the heart disease and carbohydrates, so this relation an important and need contentious investigation to functionalize this relation in improving our health.

Aim of study: To assess the relation between various measures of carbohydrate quality and incident cardiovascular disease and investigate the role of others parameters which can be affect this relation.

Key words: Carbohydrates, carbohydrate quality, diet quality, whole grains, type 2 diabetes, starch, fiber.

Introduction

Carbohydrates represent a broad group of substances that include the sugars, starches, gums and celluloses. The common attributes of carbohydrates are which contain only the elements carbon, hydrogen and oxygen, and that their combustion will yield carbon dioxide plus one or more molecules of water.

Carbohydrates are the primary source of energy in one's diet. As long as the physical activity equals the intake of carbohydrates, the metabolism is balanced. But, more often than not, it is not the case. Excess carbohydrates get stored or converted into lipids and definitely pose a threat to cardiovascular health.

Cardiovascular disease (CVD) is a general term for conditions affecting the heart or blood vessels. It's usually associated with a build-up of fatty deposits inside the arteries (atherosclerosis) and an increased risk of blood clot.

Despite significant advances in cardiovascular medicine over the past 50 y, heart disease remains the leading cause of death for both men and women in the United States ⁽¹⁾. While data from NHANES indicate a decline in the prevalence of major coronary heart disease (CHD) risk factors such as hypertension, dyslipidemia, and tobacco use ⁽²⁾, other factors such as overweight and obesity, diabetes, and the metabolic syndrome remain highly prevalent ^(3,5). Many of the chronic conditions which predispose to CHD are largely driven by unhealthy behaviors, such as poor dietary habits and physical inactivity. In fact, $\leq 80\%$ of the risk for CHD events could be attributable to a lack of adherence to a healthy lifestyle ^(6,7).

While diet has always been a major focus in the prevention of CHD, guidelines have historically emphasized a low-fat (and in particular low-saturated fat) diet ^(8,9). This has had important clinical implications as many individuals have adopted low-fat, high-carbohydrate diets in an attempt to reduce their risk for CHD. Compared with total carbohydrates, saturated fat intake was not significantly associated with CHD or cardiovascular disease outcomes. However, saturated fat was associated with increased risk of CHD compared with high-quality carbohydrates such whole grains or unsaturated fats. Although the associations between total daily carbohydrate consumption and CHD have been inconsistent,

certain sources of carbohydrates such as refined grains and added sugars have been found to be associated with CHD.

Cardiovascular disease (CVD) and diabetes are health conditions that are strongly influenced by a person's diet. Although the best diet to prevent CVD and diabetes is uncertain, reducing intake of saturated and trans unsaturated fats is known to help lower cardiovascular risk. However, even diets low in these fats can vary widely in other energy providing nutrients, particularly carbohydrates. This study will determine the effects of a higher versus lower carbohydrate diet, each with a high or low glycemic index (GI) composition, on risk factors for CVD and diabetes.

Literature review

In 2010, the American Heart Association defined an ideal diet as part of its 2020 Impact Goals. One component of the ideal diet was fiber-rich whole grains, defined as having a carbohydrate-to-fiber ratio of <10:1 ⁽¹⁰⁾. Research suggests that the measure of carbohydrate quality appears to be superior to other consumer-oriented methods for identifying a restricted set of grain foods commonly consumed in Boston-area markets ⁽¹¹⁾. In addition to that, a recent study indicated that this ratio can also be useful in evaluating the overall carbohydrate quality of the diet where it was positively associated with risk of type 2 diabetes among women ⁽¹²⁾. However, its relation to CHD outcomes has not been defined. Therefore, the purpose of the present study was to examine the association between the carbohydrate-to-fiber ratio and other measures of carbohydrate quality and quantity and incident CHD in a large cohort of US men and women.

Early prospective studies done by Morris, Garcia et al, reported the cardioprotective effect of total carbohydrate intakes and intake of dietary fiber ^(13,14,15). They were relatively underpowered and confounding of results by a range of factors certainly could not be excluded. During the past 20 years, results have been published from a substantial number of prospective studies involving cohorts of sufficient size to enable examination of potentially confounding factors. There has been particular emphasis on the cardioprotective role of cereal grains and dietary fiber. Most studies define wholegrain as either intact or milled grain with bran, germ and endosperm in the same proportion as the unmilled grain. Wholegrain foods have generally been arbitrarily defined as those foods with more than 25% wholegrain or bran content by weight ⁽¹⁶⁾. Other studies have been systematically reviewed (for example Liu, 2002; Truswell, 2002; Hu, 2003; Slavin, 2003; Flight and Clifton, 2006) ^(17,18) and meta-analysed (Anderson, 2002, 2003) ⁽¹⁹⁾. Despite the use of different instruments for assessing dietary intake, the results of the studies show a remarkably consistent trend. Meta-analysis, involving four of the largest published studies, suggested a 28% reduction in risk of CHD when comparing individuals in the highest and lowest quintiles of intake of wholegrains (relative risk 0.72, 95% confidence intervals: 0.48, 0.94) (Anderson 2003) ⁽²⁰⁾. The size of the most recent cohort studies has enabled analyses to examine the extent to which these findings might be confounded by other cardioprotective factors. While residual confounding cannot be excluded with absolute certainty, such analyses provide reasonable evidence that wholegrains protect against CHD regardless of the degree of adiposity and other measured variables associated with healthy lifestyles and eating habits.

However, it is acknowledged that people who consistently eat wholegrain breads do indeed have different lifestyles from those who do not, and it may not be possible in epidemiological studies to measure all attributes of lifestyle.

During the 1960s, Yudkin (1964) and co-workers reported strong associations between high sugar intakes and CHD. The data were cross-sectional and flawed (Keys, 1971; Truswell, 1987) ⁽²¹⁾. The Iowa Women's Health Study found no relationship between intake of sweets and desserts and CHD in over 30 000 women followed for 9 years (Jacobs et al., 1998) ⁽²²⁾. The glycaemic index (GI; and more recently the glycaemic load, GL) has provided a means of determining the extent to which carbohydrate-containing foods may determine cardiovascular risk through their potential to raise blood glucose. Liu et al. (2000b) reported from the Nurses' Health Study that women who consumed diets with a high-glycaemic load (that is high in rapidly digested starches) were at increased risk of CHD compared with those with a lower consumption; a twofold increase in risk over a 10-year follow-up was observed when comparing those in the highest and lowest quintiles of intake. The effect appeared to be independent of total energy intake and other cardiovascular risk factors ⁽²³⁾.

The joint WHO/FAO Expert Consultation on Diet, Nutrition and the Prevention of Chronic Disease (WHO Technical Report Series 916, 2003) considered that the evidence suggesting a cardio-protective effect of fruits and vegetables was 'convincing' and that relating to wholegrain cereals and NSP was 'probable'. The evidence that high intakes of total carbohydrate might increase the risk of cardiovascular diseases was considered to be 'insufficient' ⁽²⁴⁾.

In the Nurses' Health Study and the Health Professionals Follow-up Study, a statistically significant relative risk of about 1.4 was observed when comparing diabetes rates in the highest and lowest quintiles of dietary glycaemic load, after adjusting for potentially confounding factors (Salmeron et al., 1997a, 1997b). A high dietary glycaemic index was also found to be associated with an increased risk of type II diabetes in the Melbourne Collaboration Cohort Study (Hodge et al., 2004) ⁽²⁵⁾.

Women who developed gestational diabetes in the Nurses' Health Study had lower intakes of dietary fibre and higher dietary glycaemic load than those who did not (Zhang et al., 2006) ⁽²⁶⁾.

Results

During 1905,049 person-years of follow-up in the NHS there were a total of 3267 CHD events, and during 921,975 person-years of follow-up in the HPFS there were 4053 CHD events. The age-adjusted baseline characteristics of the study participants, according to quintiles of carbohydrate, starch, and cereal fiber intake. In general, men and women with higher intakes of carbohydrate and starch had higher glycemic index and glycemic load values, were more likely to have hypercholesterolemia but, were less likely to smoke, and had similar family histories of CHD to those with lower intakes of carbohydrate and starch. Men and women with higher intakes of cereal fiber were more likely to be physically active, and consumed less saturated fat and alcohol.

Significant correlations were noted in both study populations between baseline intakes of carbohydrate, starch, total fiber, cereal fiber, starch-to-total fiber ratio, starch-to-cereal fiber ratio, glycemic index, and glycemic load, with correlation coefficients ranging from -0.69 (total fiber and carbohydrate-to-total fiber ratio) to 0.95 (carbohydrates and glycemic load).

After 1,905,047 (NHS) and 921,975 (HPFS) person-years of follow-up, the study identified 7,320 cases of incident CHD. In models adjusted for age, lifestyle behaviors, and dietary variables, the highest quintile of carbohydrate intake was not associated with incident CHD (pooled-RR = 1.04; 95% CI: 0.96, 1.14; P-trend = 0.31). Total fiber intake was not associated with risk of CHD (pooled-RR = 0.94; 95% CI: 0.85, 1.03; P-trend = 0.72), while cereal fiber was associated with a lower risk for incident CHD (pooled-RR = 0.80; 95% CI: 0.74, 0.87; P-trend < 0.0001). In fully adjusted models, the carbohydrate-to-total fiber ratio was not associated with incident CHD (pooled-RR = 1.04; 95% CI: 0.96, 1.13; P-trend = 0.46). However, the carbohydrate-to-cereal fiber ratio and the starch-to-cereal fiber ratio were associated with an increased risk for incident CHD (pooled-RR = 1.20; 95% CI: 1.11, 1.29; P-trend < 0.0001).

Discussion

A growing body of literature relates various measures of carbohydrate quality to important health outcomes, including diabetes, CHD, and mortality. In this prospective cohort study, it was found the carbohydrate-to-cereal fiber ratio and the starch-to-cereal fiber ratio, but not the carbohydrate-to-fiber ratio, to be important measures of carbohydrate quality that were associated with a 20% and 17% increased risk for incident CHD, respectively. These findings were largely driven by the strong and consistent inverse association between cereal fiber intake and CHD outcomes.

There is no evidence that total daily carbohydrate or starch intake was associated with an increased risk for incident CHD. Data from the Framingham Offspring study showed an evidence for the association between the highest quintile of daily carbohydrate consumption and low HDL and high triglycerides, known risk factors for CHD ⁽²⁷⁾. Similarly, data from the Shanghai Men's and Women's Health Study showed that the highest quartile of daily carbohydrate intake was associated with a nearly 3-fold increase in risk for incident CHD ⁽²⁸⁾. Conversely, and consistent with our findings, the Singapore Chinese Health Study showed no evidence of increased risk for CHD according to total daily carbohydrate and starch intake. The Prospective Urban Rural Epidemiology (PURE) study, a prospective cohort study with 135,335 participants from 18 countries, has found that participants with the highest carbohydrate intake (77% of daily energy intake) did not have a higher risk of cardiovascular disease than did those at the lowest quintile of intake (46% of daily energy intake). However, this study and the PURE study cannot be compared because most participants of the PURE study were in low-

income countries where the diet was heavily composed of carbohydrates from refined sources such as white rice—a characteristic of poverty diets, which are also high in sodium and low in animal fat and vegetable oils, and therefore the individual effects of diet and poverty cannot be separated. The inconsistent findings between carbohydrate intake and CHD risk may reflect the dietary fiber and whole-grain content of the diet in the aforementioned study populations.

In the NHS, it found that total daily fiber and cereal fiber were associated with an 18% and 33% reduced risk for CHD, respectively. In the HPFS, only cereal fiber was significantly and inversely associated with CHD risk. These findings are consistent with a recent meta-analysis of 17 cohort studies involving >900,000 participants where the highest tertial of dietary fiber intake was associated with a 16% reduced risk of all-cause mortality ⁽²⁹⁾. Fruit and vegetable fiber, however, were not associated with a significantly reduced risk for CHD in our combined populations. These findings are similar to prior published data from the HPFS, where fruit and vegetable fiber were not associated with a reduced risk of CHD. The lack of association between fruit and vegetable fiber and risk of CHD could be because fiber in fruits and vegetables works synergistically with the other components of the whole foods, which could explain the limited benefit of isolated or synthetic fiber compared with whole foods such as fruits and vegetables.

In addition to the inverse association of daily fiber intake and CHD, and in particular cereal fiber, we found the carbohydrate-to-cereal fiber ratio and the starch-to-cereal fiber ratio to be important measures of carbohydrate quality as it relates to CHD. These ratios likely reflect the extent to which fiber and whole grains are present in the diet. This is consistent with a large body of evidence linking whole-grain

consumption with important health outcomes ⁽³⁰⁾. Recently, the Scandinavian HELGA cohort observed a 32% reduction in all-cause mortality for women and a 25% reduction in all-cause mortality for men in the highest compared with the lowest quartile of whole-grain product consumption. Similar associations between whole-grain intake and all-cause mortality were noted in prior publications involving the HPFS, and with CHD events in the NHS. A recent meta-analysis of 18 studies involving >14,000 patients also found whole-grain consumption to be associated with a 21% reduced risk for CHD. Much of the benefits from some whole grains could be completely attributable to the cereal content, but more detailed feeding studies with exact measures of intake may be necessary to tease out the factors most responsible for the beneficial effect of cereal whole grains.

Other measures of carbohydrate quality also have strong associations with CHD risk. Prior data from the NHS suggest that diets with a high glycemic load are associated with a nearly 2-fold increased risk for incident CHD ⁽³¹⁾. Similarly, in a meta-analysis of 37 prospective cohort studies, diets with a high glycemic index and glycemic load were both associated with an increased risk for a number of chronic diseases including diabetes and CHD. Taken together, these findings suggest a robust relation between measures of carbohydrate quality and CHD.

A number of potential mechanisms explain how carbohydrate quality measures, such as the carbohydrate-to-cereal fiber ratio and the starch-to-cereal fiber ratio, are associated with CHD risk. First, low ratios are consistent with a diet rich in fiber and whole grains. Such diets have been shown to improve postprandial glucose and insulin responses, enhance satiety, and reduce overall energy intake. In related work, data from the

Multi-Ethnic Study of atherosclerosis (MESA) study showed that diets rich in whole grains were inversely associated with obesity, insulin resistance, inflammatory markers, elevated fasting glucose, and incident diabetes. Conversely, when diets are lacking adequate fiber and whole grains, there is an increased risk for diabetes. Recent work involving >70,000 participants in the NHS found that diets high in refined grains (defined by high carbohydrate-to-cereal fiber and starch to cereal fiber ratios) were associated with a 28% and 39% increased risk of incident type 2 diabetes mellitus, respectively. Cardiometabolic risk related to a diet high in refined grains has also been associated with other potent risk factors for CHD, including hypertension, dyslipidemia, and impaired fibrinolysis ⁽³²⁾.

So, the previous studies confirm the consistent association between dietary fiber, especially cereal fiber and risk for CHD. Furthermore, although the positive association between the carbohydrate-to-cereal fiber ratio and the starch-to-cereal fiber ratio and risk of CHD was mainly driven by cereal fiber, the ratios were predictive of risk of type 2 diabetes in a previous study and warrant further research in relation to health endpoints in diverse populations. Given these associations, future work should focus on how these global measures of carbohydrate quality are related to the primary and secondary prevention of CHD.

Conclusion

Dietary cereal fiber appears to be an important component of carbohydrate quality. The carbohydrate-to-cereal fiber ratio and the starch-to-cereal fiber ratio, but not the carbohydrate-to-fiber ratio, was associated with an increased risk for incident CHD. This trial was registered at clinicaltrials.gov as NCT03214861. *Am J Clin Nutr* 2018;107:257–267.

These cross-sectional findings support the hypothesis that a high GI diet unfavorably affects CVD risk factors and therefore, substitution of high with low GI dietary carbohydrates may have reduce the risk of CVD.

Whole grains, fruits, and vegetables and an overall low GL diet appear to reduce the risk of CVD and type 2 diabetes in men and women of all ages. Dietary approaches to risk reduction may be particularly effective among the most susceptible individuals—those who are overweight and insulin resistant. The recommendation to follow a diet that includes an abundance of fiber rich foods in order to prevent CVD and diabetes is based on a wealth of consistent scientific evidence.

Low glycaemic index foods may confer benefits in terms of lowering total cholesterol and improving glycaemic control in people with diabetes. However, it is not clear whether these benefits are independent of the effects of dietary fibre or the fact that low glycaemic index foods tend to have intact plant cell walls. Furthermore, it is uncertain whether functional and manufactured foods with a low glycaemic index confer the same long-term benefits as low glycaemic index predominantly plant-based foods.

Recently reported that a high dietary GI was associated with a higher prevalence of the metabolic syndrome in the Framingham Offspring Cohort, while neither total carbohydrate intake nor dietary GL were associated with this syndrome.

References

- 1- Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, de Ferranti S, Despres J-P, Fullerton HJ, Howard VJ, et al. Heart disease and stroke statistics 2015 update: a report from the American Heart Association. *Circulation* 2015 Jan 27;131(4):e29–e322.
- 2- Huffman MD, Capewell S, Ning H, Shay CM, Ford ES, Lloyd-Jones DM. Cardiovascular health behavior and health factor changes (1988-2008) and projections to 2020: results from the National Health and Nutrition Examination Surveys. *Circulation* 2012 May 29;125(21):2595–602.
- 3- Yang L, Colditz GA. Prevalence of overweight and obesity in the United States, 2007–2012. *JAMA Intern Med* 2015;175(8):1412–1413.
- 4- Long-Term Trends in Diagnosed Diabetes. CDC's Division of Diabetes Translation. National Diabetes Surveillance System. 2011. <http://www.cdc.gov/diabetes/statistics>
- 5- Mozumdar A, Liguori G. Persistent increase of prevalence of metabolic syndrome among U.S. adults: NHANES III to NHANES 1999–2006. *Diabetes Care* 2011 Jan;34(1):216–9.
- 6- Stampfer MJ, Hu FB, Manson JE, Rimm EB, Willett WC. Primary prevention of coronary heart disease in women through diet and lifestyle. *N Engl J Med* 2000 Jul 6;343(1):16–22.
- 7- Akesson A, Larsson SC, Discacciati A, Wolk A. Low-risk diet and lifestyle habits in the primary prevention of myocardial infarction in men: a population-based prospective cohort study. *J Am Coll Cardiol* 2014 Sep 30;64(13):1299–306.

8- US Department of Agriculture and the US Department of Health and Human Services. Nutrition and your health. Dietary guidelines for Americans. 1980.

9- US Department of Agriculture and the US Department of Health and Human Services. Dietary Guidelines for Americans. 7th ed, Washington (DC): US Government Printing Office; 2010.

10- Lloyd-Jones DM, Hong Y, Labarthe D, Mozaffarian D, Appel LJ, Van Horn L, Greenlund K, Daniels S, Nichol G, Tomaselli GF, et al. on behalf of the American Heart Association Strategic Planning Task F, Statistics C. Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's strategic impact goal through 2020 and beyond. *Circulation* 2010 Feb 2;121(4):586–613.

11- Mozaffarian RS, Lee RM, Kennedy MA, Ludwig DS, Mozaffarian D, Gortmaker SL. Identifying whole grain foods: a comparison of different approaches for selecting more healthful whole grain products. *Public Health Nutr* 2013 Dec;16(12):2255–64.

12- AlEssa H, Bhupathiraju S, Malik V, Wedick N, Campos H, Rosner B, Willett W, Hu FB. Carbohydrate quality and quantity and risk of type 2 diabetes in US women. *Am J Clin Nutr* 2015 Dec;102(6):1543–53.

13- McGee DL, Reed DM, Yano K, Kagan A, Tillotson J (1984). Ten-year incidence of coronary heart disease in the Honolulu Heart Program: relationship to nutrient intake. *Am J Epidemiol* 119(5), 667–676.

14- Garcia-Palmieri MR, Sorlie P, Tillotson J, Costas Jr R, Cordero E, Rodriguez M (1980). Relationship of dietary intake to subsequent

coronary heart disease incidence: The Puerto Rico Heart Health Program. *Am J Clin Nutr* 1980 Aug; 33(8), 1818–1827.

15- Morris JN, Marr JW, Clayton DG (1977). Diet and heart: a postscript. *BMJ* 1977 Nov 19; 2(6098), 1307–1314.

16- Flight I, Clifton P (2006). Cereal grains and legumes in the prevention of coronary heart disease and stroke: a review of the literature. *Eur J Clin Nutr* 2006 Oct; 60(10), 1145–1159.

17- Liu S, Manson JE, Stampfer MJ et al. (2000). A prospective study of whole-grain intake and risk of type 2 diabetes mellitus in US women. *Am J Public Health* 90(9), 1409–1415.

18- Truswell AS (2002). Cereal grains and coronary heart disease. *Eur J Clin Nutr* 2002 Jan;56(1): 1–14.

19- Anderson JW (2002). Whole-grains intake and risk for coronary heart disease. In: Marquart L, Slavin JL, Fulcher RD (eds). *Whole-grain Foods in Health and Disease*. American Association of Cereal Chemists. St Paul: Minnesota, USA. pp 187–200.

20- Anderson JW (2003). Whole grains protect against atherosclerotic cardiovascular disease. *Proc Nutr Soc* 62(1), 135–142.

21- Yudkin J (1964). Dietary fat and dietary sugar in relation to ischaemic heart disease and diabetes. *Lancet* 4;2(7349): 4–5.

22- Jacobs Jr DR, Meyer KA, Kushi LH, Folsom AR (1998). Whole-grain intake may reduce the risk of ischemic heart disease death in post-menopausal women: the Iowa Women's Health Study. *Am J Clin Nutr* 68(2), 248–257.

- 23- Liu S, Willett WC, Stampfer MJ, Hu FB, Franz M, Sampson L et al. (2000b). A prospective study of dietary glycaemic load, carbohydrate intake, and risk of coronary heart disease in US women. *Am J Clin Nutr* 2000Jun; 71(6), 1455–1461.
- 24- WHO Technical Report Series 916 (2003). Diet, nutrition and the prevention of chronic diseases. Report of a Joint WHO/FAO Expert Consultation (Geneva).
- 25- Hodge AM, English DR, O’Dea K et al. (2004). Glycaemic Index and dietary fiber and the Risk of type 2 diabetes. *Diabetes Care* 2004 Nov; 27(11), 2701–2706.
- 26- Zhang C, Liu S, Solomon CG et al. (2006). Dietary fiber intake, dietary glycemic load and the risk for gestational diabetes mellitus. *Diabetes Care* 2006 Oct;29(10), 2223–2230.
- 27- McKeown NM, Meigs JB, Liu S, Rogers G, Yoshida M, Saltzman E, Jacques PF. Dietary carbohydrates and cardiovascular disease risk factors in the Framingham offspring cohort. *J Am Coll Nutr* 2009 Apr;28(2):150–8.
- 28- Yu D, Shu XO, Li H, Xiang YB, Yang G, Gao YT, Zheng W, Zhang X. Dietary carbohydrates, refined grains, glycemic load, and risk of coronary heart disease in Chinese adults. *Am J Epidemiol* 2013 Nov 15;178(10):1542–9.
- 29- Yang Y, Zhao L-G, Wu Q-J, Ma X, Xiang Y-B. Association between dietary fiber and lower risk of all-cause mortality: a meta-analysis of cohort studies. *Am J Epidemiol* 2015 Jan 15;181(2):83–91.

30- Zong G, Gao A, Hu FB, Sun QS. Whole grain intake and mortality from all causes, cardiovascular disease, and cancer: a meta-analysis of prospective cohort studies. *Circulation* 2016 Jun 14;133(24):2370–80.

31- Barclay AW, Petocz P, McMillan-Price J, Flood VM, Prvan T, Mitchell P, Brand-Miller JC. Glycemic index, glycemic load, and chronic disease risk - a meta-analysis of observational studies. *Am J Clin Nutr* 2008 Mar;87(3):627–37.

32- Ferrannini E, Buzzigoli G, Bonadonna R, Giorico MA, Oleggini M, Graziadei L, Pedrinelli R, Brandi L, Bevilacqua S. Insulin resistance in essential hypertension. *N Engl J Med* 1987 Aug 6;317(6):350–7.