PACIFIC HEALTH DIALOG
MARCH 2014 · VOLUME 20 · NUMBER 1

STUDY

Fat Storage Syndrome in Pacific Peoples: a combination of environment and genetics?

Johnson R J[1,2], Lanaspa M A[1], Sanchez-Lozada L G[3,4], Rivard C J[1], Bjornstad P[5], Merriman T R[6], and Sundborn G[7]

ABSTRACT

Pacific people (especially Micronesian and Polynesian) have some of the highest rates of obesity and diabetes in the world that largely developed since the introduction of western culture and diet. Recent studies suggest that much of the risk relates to the excessive intake of sugar (sucrose) and carbohydrates, leading to a type of fat storage syndrome (metabolic syndrome). Here we discuss some of the environmental, genetic and epigenetic reasons why this group might be especially prone to developing obesity and diabetes compared to other ethnic groups. Indirect evidence suggests that the higher endogenous uric acid levels in the Polynesian-Micronesian population may represent a predisposing factor for the development of obesity and diabetes in the context of Western diets and lifestyles. Pacific people may be an ideal group to study the role of "thrifty genes" in the pathogenesis of the current obesity epidemic.

Key words: *Sucrose, Fructose, Fat Storage Syndrome, Metabolic syndrome, Diabetes, Pacific Islanders, Polynesians, Uric acid*

AUTHOR AFFILIATIONS:

From the [1]Division of Renal Diseases and Hypertension, University of Colorado; [2]Division of Nephrology, Eastern Colorado Health Care System, Department of Veteran Affairs, Denver, CO 80220 [3]Dept. of Nephrology, INC Ignacio Chávez, Mexico City. Mexico; [4]Lab of Renal Physiopathology, INC Ignacio Chávez, Mexico City, Mexico; [5]Division of Endocrinology, Children's Hospital, University of Colorado; [6]Department of Biochemistry, University of Otago, Dunedin, New Zealand; ; [7]Section of Epidemiology and Biostatistics, University of Auckland, Auckland, New Zealand.

Introduction

Few populations have suffered more from the worldwide epidemic of obesity and diabetes than the indigenous and migrant populations of Pacific Island nations. In a report by the World Health Organization from 2007, of the 10 most obese countries in the world, eight are from the Pacific Islands (Figure 1). The rise in diabetes has been meteoric. In Nauru, for example, the first recorded case of diabetes was diagnosed in 1925[1], whereas by 1979, 40 percent of the population suffered from this debilitating condition[2]. Obesity carries a greater toll than simply the excess weight one is forced to carry, for it comes with its evil partners of high blood pressure, dyslipidemias, strokes, heart disease and chronic kidney and liver disease. If there was ever a puzzle to solve, this is the one that health care providers need to focus on.

In this brief review, we will address what has emerged as one of the greatest risk factors for the development of obesity and diabetes, that being the intake of excessive amounts of fructose, primarily from the intake of sugar (sucrose). We will also take an evolutionary biological perspective to develop a better understanding of why this particular group may be at such high risk.

Fat Storage Syndrome, Fructose, and the Roots of the Obesity and Diabetes Epidemic

While specialists often tend to focus on their particular disease, there is increasing evidence that many of the most common diseases facing us today have their roots in the physiological response of fat storage (Figure 2)[3,4]. In essence, one of the basic rules of survival is to find ways to live through periods of food shortage, and to do this many animals will activate metabolic processes that lead to conservation of energy, reduction in metabolism, and the storage of fat in their liver and adipose

tissues[3,4]. Accompanying this process is the development of insulin resistance, which allows maintenance of circulatory glucose levels that provide fuel for the brain[3,4]. These physiological features are called the metabolic syndrome in humans and often are considered to be pathophysiological[5], but they represent normal physiological processes that can be observed in hibernating mammals and long distance migrating birds[3,4]. As such, we prefer to call it fat storage syndrome to characterize its underlying physiology[3].

Weight is tightly regulated in most animal species, and evidence suggests that to initiate fat storage, one has to activate a specific metabolic program[6-8]. First, one must block normal satiety responses, such as by inducing leptin resistance[9], or by stimulating the craving or addiction to certain foods[10,11]. One must also try to reduce energy expenditure by decreasing physical activity and metabolism[3,4]. This is commonly done by animals preparing for hibernation, estivation, or long distance migration[3].

The net effect is to stimulate excessive food intake (hyperphagia) and reduce metabolism, leading to weight gain. A key aspect to understanding this process is that many features of western culture, such as the providin provision of excessive portions of food or the increasing use of television, are likely the response to activation of this metabolic switch[3,4]. This is not to revoke the idea that these social stimuli are not playing a significant contributory role in the epidemic, but rather to emphasize that the underlying driving mechanism may be mediated by metabolic and neuroendocrine-driven mechanisms to store fat.

Another insight has been the activation of the process which occurs in the mitochondria, the key organelle governing energy metabolism. Studies by our group and others suggest that the initiating mechanism is the induction of mitochondrial oxidative stress that leads directly to activation of fat synthesis and a blockade in fatty acid oxidation[12]. In addition, there is the activation of a 'switch' in which adenosine monophosphate (AMP) is preferentially shunted for utilization by AMP deaminase (AMPD), as opposed to being used to engage the activation of AMP activated-protein kinase (AMPK)[13]. Activation of AMPD leads to the generation of uric acid that has a central role in driving these metabolic processes[12-14]. The changes in mitochondrial metabolism can result in changes in body composition (increasing fat) and the development of insulin resistance even in the absence of increased caloric intake of weight gain[15-17]. Thus, the process activating the storage of fat results in both calorie-dependent (weight gain) and calorie-independent (body composition and insulin resistance) effects[17].

Experimental studies suggest that intake of certain foods might have a major role in activating the metabolic processes leading to fat storage. Fructose, present in added sugars such as sucrose and high fructose corn syrup, has been strongly implicated as the major food source activating this process[17,18]. Fructose has been shown to specifically activate AMP deaminase and to induce mitochondrial oxidative stress[13,19], activating the full phenotypic presentation of the fat storage syndrome, and leading to its downstream consequences, including diabetes, fatty liver and steatohepatitis, hypertension and chronic kidney disease[17,20-25]. Natural fruits containing fructose can also engage this pathway, but are relatively less effective due to the relatively lower fructose content (per fruit) and the presence of other ingredients in fruit (fiber, antioxidants, etc) that help prevent the induction of mitochondrial oxidative stress[26,27]. Theoretically, other foods, such as purine-rich beer and umami foods, may also engage the stimulation of fat storage by providing substrates that might increase intracellular uric acid levels[28]. Finally, genetic and epigenetic mechanisms might also have a role in activating these metabolic pathways that would favor the storage of fat (to be discussed later).

The Epidemiological Transition: Role of Sugar in the Epidemic of Obesity in Pacific People

Sugar (sucrose) consists of a disaccharide of fructose and glucose, and like fructose, can induce features of fat storage syndrome in experimental animals[29]. Sucrose can rapidly induce addiction in rats, due to the repeated stimulation of dopamine in the brain followed by a chronic decrease in dopamine (D2) receptors[30]. Because the cellular and mitochondrial activation of the fat storage switch is driven by the concentrations of fructose, both the amount and rapidity by which sucrose is ingested should be important. Hence, sugar-sweetened beverages such as soft drinks, sweetened teas, and energy drinks become the best way to activate the fat switch. Consistent with this finding, is the intake of soft drinks i as a major risk factor for the development of metabolic syndrome and diabetes[31-36].

Figure 1. Countries with the Top Rates of Obesity or Overweight#

1.	Nauru*	94.
2.	Federated States of Micronesia*	91.
3.	Cook Islands**	90.
4.	Tonga**	90.
5.	Niue**	81.
6.	Samoa**	80.
7.	Palau*	78.
8.	Kuwait	74.
9.	United States	74.
10.	Kiribati*	73.

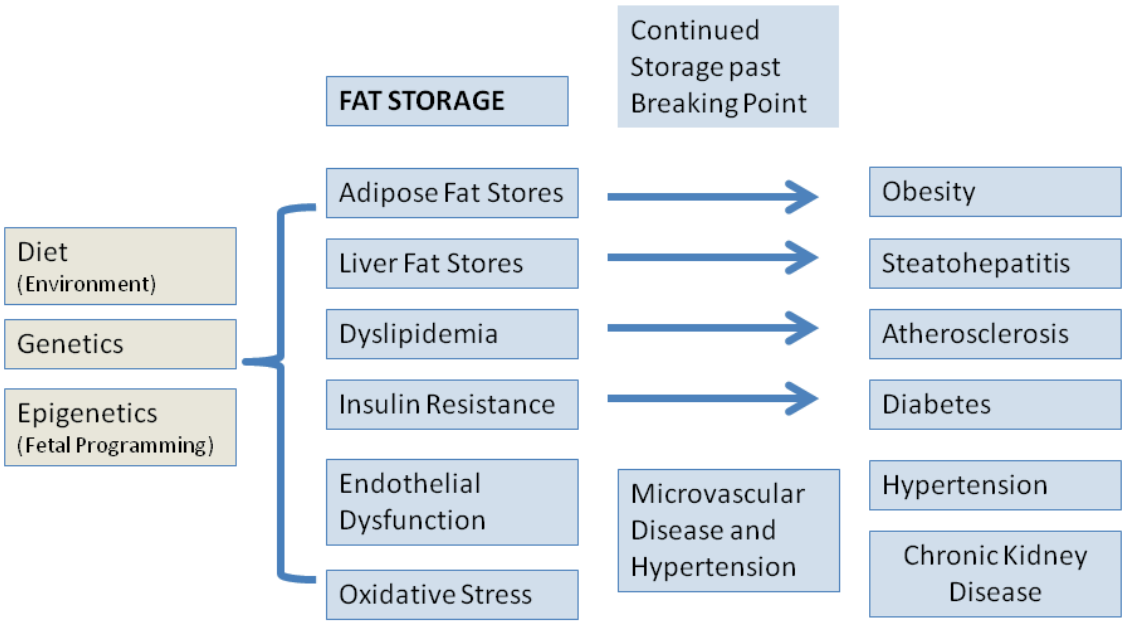
Key: #Based on World Health Organization Report; *Micronesia, **Polynesia

The rise in world sugar production in the eighteenth and nineteenth centuries led to a marked rise in sugar intake, especially in England and the United States[4,37]. This was further stimulated by the progressive reduction in the English tax on sugar during the nineteenth century, resulting in its full repeal in April, 1874. As such, sugar became one of the best items for trade when westerners would meet indigenous peoples. This was particularly true in the Pacific Islands. In Nauru, for example, sugar intake increased markedly with its introduction by westerners, with one report suggesting that

the mean intake per person may have reached one pound of sugar per day by 1927[1,38]. Sugar was also a major trading product introduced to the New Zealand Māori, as well as to other Polynesian communities such as Samoa and Tonga. Today, intake of soft drinks and sugar remains very high among these ethnic groups[2]. Numerous reasons may help explain this, including the fact that soft drinks are addictive and inexpensive, and because the hot climate encourages the intake of fluids.

One should mention that other foods may also be contributory. Recently our group showed that glucose can also stimulate fatty liver and insulin resistance if it is converted to fructose in the liver[16]. The conversion of glucose to fructose is mediated by aldose reductase, which is normally not expressed but may be induced by high glucose solutions (such as soft drinks), by high salt diets, or by recurrent dehydration (such as may occur in hot environments)[16,39]. If this process is activated, then high glycemic foods such as flour and rice might also engage the pathway[40]. High fat foods may also synergize with sugar to drive weight gain and fatty liver[41]. In addition, alcohol and especially beer (which contains high purine content from the brewer's yeast) also could engage the pathway[28]. However, given the powerful effects of fructose, it is likely that the major driving stimulus is fructose intake from excessive sugar ingestion.

Figure 2. Fat Storage Syndrome as a Precursor for Obesity, Diabetes and Cardiovascular Disease



Role of Genetics and Epigenetics in the Epidemic of Obesity in Pacific People

The anthropologist, James Neel, proposed over 50 years ago that the rise in obesity and diabetes in modern culture may have represented the acquisition of "thrifty genes" that would favor fat storage during a period of famine, but with the consequences of causing obesity and diabetes during a time of plenty[42]. The discovery that uric acid is an important regulator of mitochondrial oxidative stress and fat storage led our group to suggest that the higher levels of uric acid in humans and apes compared to other mammals may have the consequence of increasing our susceptibility for becoming fat[43-45]. Indeed, humans have a higher serum uric acid level due to an absence of uricase, which is an enzyme present in many animals that degrades uric acid. Interestingly, humans lost uricase during the mid-Miocene, at a time when our ancestors were facing extinction due to changing climates and reduced availability of fruits (which were their major food supply)[46,47]. In collaboration with Dr Peter Andrews, we have suggested that the loss of uricase may have provided a survival advantage by increasing intracellular uric acid levels that would help stimulate fat storage[45]. Indeed, we have shown that rats that have uricase inhibited developed worse features of metabolic syndrome in response to the same dose of fructose[48]. Furthermore, in collaboration with Dr Eric Gaucher, we have resurrected the extinct ape uricase based on computer modeling of uricases from living species and have shown that its presence blocks the increase in fat that occurs in liver cells exposed to fructose[49]. Thus, it seems likely that the loss of uricase may have acted as a "thrifty gene" to increase our susceptibility to the effects of sugar.

Pacific people consist of three major ancestral groups (Polynesians, Micronesians, and Melanesians). While all three groups are being affected by the epidemic of obesity and diabetes, the hardest hit groups are the Micronesians (such as those living in Nauru) and the Polynesians (including the New Zealand Māori)[2]. Genetic studies suggest the Micronesians and Polynesians are closely related, and that they originated from aborigines in Taiwan[50]. Approximately 3000 years ago they passed through Melanesia, colonizing off-shore islands, on their way to the more distant Pacific Islands, which they reached in only the last 800 to 900 years[50]. While there was some admixing with the Melanesians[51], in general Polynesians are genetically very distinct from that population[50]. Interestingly, the serum uric acid levels in Taiwanese aborigines, Micronesians and Polynesians appear to be higher than that observed in many other ethnic groups[52-54]. The Taiwanese aboriginal population

also suffers from higher rates of obesity and diabetes than the Han Chinese living in Taiwan[55]. While some of these studies might reflect the additive effects of diets high in carbohydrates and sugar[56], there is also some evidence that uric acid levels were high when these populations were on their native diets[57,58]. For example, we found that Yanomamö Indians on their native diets have uric acid levels in the 3 to 4 mg/dl range[59], whereas Prior et al reported that Polynesians living on native diets of coconut, taro and fish in Pukapuka had uric acid levels of 7 mg/dl or greater[60]. Evans further showed that the elevated uric acid levels in the population on Pukapuka correlated with obesity, as measured by a ponderal index[57]. Further evidence that the high uric acid levels may have been present in Polynesian has been provided by the discovery of gouty lesions in skeletons identified from early Māori culture i of Wairau Bar, New Zealand, circa 1200 A.D., as well as other early Polynesian (Lapitan) sites[61-63]. Gouty lesions have also been identified in skeletons of ancestral Micronesians[64].

The higher uric acid levels in Polynesians prior to westernization likely has a genetic basis, but could potentially reflect diet, as their intake included purine-rich seafood, and foods containing fructose, such as roots from the New Zealand Cabbage (Cordyline australis) and the Pacific cabbage (Cordyline terminalis) tree, and the karaka fruit (Corynocarpus laevigata)[58]. Some of the elevation of uric acid levels in current Micronesians and Polynesians may also reflect the introduction of western diet, such as sugarcane. Alcohol intake may also account for higher uric acid levels in some of the population[65,66]. However, it seems likely that the Micronesian-Polynesian population express additional polymorphisms in uric acid metabolism besides the uricase mutation that may be responsible for the higher serum uric acid levels. For example, one study in Taiwanese aborigines linked hyperuricemia to chromosome 4q25[54]. Other associations with urate transporters in Polynesians have also been identified[67]. A number of polymorphisms in uric acid metabolism have been linked with features of metabolic syndrome, including genes involved in fructose and glucose metabolism, aldose reductase, xanthine oxidase, and urate transport[68-72]. Epigenetic mechanisms may also be involved. Maternal malnutrition and low birth weights are also associated with the development of metabolic syndrome, and they also lead to an increase in serum uric acid that manifests early in the infant (reviewed in [73]).

We propose that the Polynesian and Micronesian peoples may have an additional reason to be susceptible to obesity due to the acquisition of genetic polymorphisms and/or epigenetic modifications that led to a higher endogenous uric acid level above and beyond that which occurs with simple genetic deletion of uricase. The ability to sail for days to distant islands and to live on the limited resources of the island may have provided a survival advantage to those individuals who harbored a polymorphism favoring higher uric acid levels. The decimation of up to half of those of Polynesian ancestry with the initial introduction of diseases including small pox, influenza and measles[2] might also have favored the survival of individuals having higher uric acid levels and greater fat stores. The widespread viewpoint among early Polynesians that obese individuals were more attractive[1] may have been a response to the benefits of fat stores on successful pregnancy[74] and might have provided a social determinant that would also favor selection of an obese phenotype. A higher uric acid level may not only favor fat accumulation, but also the preservation of nitrogen due to its ability to block urea synthesis[75].

Caveats

One might argue that if uric acid was so important in driving obesity and diabetes, and if uric acid levels were indeed higher in the Micronesian and Polynesian population for centuries, that these conditions should have been present before the introduction of western culture. Obesity was known to early Polynesians, and was in fact coveted, likely because pregnancy is tightly linked with adequate fat stores[74]. Diamond mentions that early explorers commented that Nauruans were "plump"[1]. On reviewing historic images of Māori (1870) and Nauruan (1916) people, there is evidence of some individuals being overweight or obese (see The Natural Heritage Collection of New Zealand (www.nhc.net.nz) and photos from the National Archives of Australia, especially by Thomas McMahon).

However, diabetes and other complications appear to have been rare. This may relate to the necessity to maintain physical activity for their daily living. While obesity is commonly accompanied by decreased activity (which appears to be metabolically driven), the encouragement of active exercise can reduce weight and the risk for diabetes[76].

Another concern relates to recent studies investigating uric acid polymorphisms in Māori and other Pacific Island populations. These studies have identified polymorphisms in SLC2A9 as being one of the reasons for higher uric acid levels and increased risk for gout in this population[77]. However, while polymorphisms in SLC2A9 increase the risk for serum uric acid levels and gout, they do not appear to increase the risk for obesity, diabetes, or cardiovascular disease[78,79]. Notwithstanding this, recent studies suggest that SLC2A9 is quite complicated, as systemic knockdown causes hypouricemia[80], but knockdown of intestinal SLC2A9 causes hyperuricemia and obesity that is uric acid-dependent (Brian DeBosch, Washington University, personal communication). Hence, polymorphisms that increase serum uric acid might actually lower uric acid levels entering the liver, and might even block the effects of fructose. Indeed, recent studies suggest that the presence of SLC2A9 polymorphisms that increase serum uric acid might actually blunt the risk for soft drink intake to increase the risk of gout[81].

Finally, these studies do not rule out other potential genetic mechanisms for why Polynesians and Micronesians show increased susceptibility to obesity. For example, polymorphisms in the leptin gene have been linked with obesity in Samoans[82]. A recent sequencing of the mitochondrial genome also identified novel variants specific to the Polynesian population[83].

Another potential confounding factor is the fact that, while serum uric acid is elevated in subjects with prediabetes and is a strong predictor of diabetes[17], serum uric acid levels fall when a subject becomes diabetic[84,85]. The mechanism is not clear, but may be mediated partially by the effects of glycosuria to stimulate uricosuria. As such, studies investigating uric acid levels and their relationship to cardiovascular effects have to carefully control for the presence or absence of diabetes.

Additional Mechanisms Involved in the Obesity Epidemic in Pacific Peoples

With globalization and increased international trade, many

Pacific nations are now the recipients of many substandard nutritional products from wealthier Western and Asian countries[86,87]. For example New Zealand and the US export unhealthy meat products of which there is limited demand for on their domestic markets such as lamb flaps (ribs of the lamb), lard, and turkey tails to Pacific Island nations[88,89]. Many soft-drink companies not only export to, but also produce their beverages in these countries due to the low cost of labor[90]. The net result of this has been described as an exportation of non-communicable diseases from wealthier nations to the Pacific[91,92]. Furthermore, migrant Polynesian populations tend to be located at the lower end of the socio-economic profile in their new countries meaning that they are more likely to have an unhealthier nutritional profile[93,94]. These factors, combined with the greater genetic susceptibility to fat accumulation in response to sugar intake described in this paper, place Pacific populations (both indigenous and migrant) at greater risk of diabetes and metabolic disorders than other population groups and may explain the higher prevalence of both unhealthy weight and diabetes observed.

Conclusion

Obesity and diabetes have become rampant in the Pacific nations, as well as in migrant Pacific populations in western countries. The prevalence of obesity and diabetes in these groups represent some of the highest in the world. Understanding the cause of this epidemic remains a major goal for clinical medicine and public health. Recent studies suggest that excessive intake of sugar, especially in the form of soft drinks, is likely the primary mechanism driving the epidemic. Genetic and epigenetic mechanisms are likely involved, and continued attention should focus on the reasons why Polynesians and Micronesians have higher serum uric acid levels. At the core, public health policy should focus on reducing soft drink intake and following the American Heart Association guidelines for intake of added sugars[95]. Given the difficulty to persuade the general populace to reduce sugar intake voluntarily, measures such as improved education, better labeling, warning labels and taxes on soft drinks should be considered.

References

1. Diamond J. The double puzzle of diabetes. Nature 2003;423:599-602.

2. Zimmet P. Epidemiology of diabetes and its macrovascular manifestations in Pacific populations: the medical effects of social progress. Diabetes Care 1979;2:144-53.

3. ohnson RJ, Stenvinkel P, Martin SL, et al. Redefining metabolic syndrome as a fat storage condition based on studies of comparative physiology. Obesity (Silver Spring) 2013;21:659-64.

4. Johnson RJ. The Fat Switch. Hoffman Estates: mercola.com; 2012.

5. Reaven GM. Banting Lecture 1988. Role of insulin resistance in human disease. 1988. Nutrition 1997;13:65; discussion 4, 6.

6. Keesey RE, Hirvonen MD. Body weight set-points: determination and adjustment. J Nutr 1997;127:1875S-83S.

7. Keesey RE, Powley TL. Body energy homeostasis. Appetite 2008;51:442-5.

8. Bairlein F. How to get fat: nutritional mechanisms of seasonal fat accumulation in migratory songbirds. Naturwissenschaften 2002;89:1-10.

9. Correia ML, Haynes WG. Leptin, obesity and cardiovascular disease. Curr Opin Nephrol Hypertens 2004;13:215-23.

10. Avena NM, Rada P, Hoebel BG. Sugar and fat bingeing have notable differences in addictive-like behavior. J Nutr 2009;139:623-8.

11. Blumenthal DM, Gold MS. Neurobiology of food addiction. Curr Opin Clin Nutr Metab Care 2010;13:359-65.

12. Lanaspa MA, Sanchez-Lozada LG, Choi YJ, et al. Uric acid induces hepatic steatosis by generation of mitochondrial oxidative stress: potential role in fructose-dependent and -independent fatty liver. The Journal of biological chemistry 2012;287:40732-44.

13. Lanaspa MA, Cicerchi C, Garcia G, et al. Counteracting Roles of AMP Deaminase and AMP Kinase in the Development of Fatty Liver. PloS one 2012;7:e48801.

14. Lanaspa MA, Sanchez-Lozada LG, Cicerchi C, et al. Uric Acid stimulates fructokinase and accelerates fructose metabolism in the development of Fatty liver. PloS one 2012;7:e47948.

15. Ishimoto T, Lanaspa MA, Le MT, et al. Opposing effects of fructokinase C and A isoforms on fructose-induced metabolic syndrome in mice. Proceedings of the National Academy of Sciences of the United States of America 2012;109:4320-5.

16. Lanaspa MA, Ishimoto T, Li N, et al. Endogenous fructose production and metabolism in the liver contributes to the development of metabolic syndrome. Nat Commun 2013;4:2434.

17. Johnson RJ, Nakagawa T, Sanchez-Lozada LG, et al. Sugar, uric Acid, and the etiology of diabetes and obesity. Diabetes 2013;62:3307-15.

18. Johnson RJ, Perez-Pozo SE, Sautin YY, et al. Hypothesis: could excessive fructose intake and uric acid cause type 2 diabetes? Endocr Rev 2009;30:96-116.

19. van den Berghe G, Bronfman M, Vanneste R, Hers HG. The mechanism of adenosine triphosphate depletion in the liver after a load of fructose. A kinetic study of liver adenylate deaminase. Biochem J 1977;162:601-9.

20. Ishimoto T, Lanaspa MA, Rivard CJ, et al. High fat and high sucrose (western) diet induce steatohepatitis that is dependent on fructokinase. Hepatology 2013.

21. Roncal-Jimenez CA, Lanaspa MA, Rivard CJ, et al. Sucrose induces fatty liver and pancreatic inflammation in male breeder rats independent of excess energy intake. Metabolism: clinical and experimental 2011;60:1259-70.

22. Stanhope KL, Schwarz JM, Keim NL, et al. Consuming fructose-sweetened, not glucose-sweetened, beverages increases visceral adiposity and lipids and decreases insulin sensitivity in overweight/obese humans. J Clin Invest 2009;119:1322-34.

23. Perez-Pozo SE, Schold J, Nakagawa T, Sanchez-Lozada LG, Johnson RJ, Lillo JL. Excessive fructose intake induces the features of metabolic syndrome in healthy adult men: role of uric acid in the hypertensive response. Int J Obes (Lond) 2010;34:454-61.

24. Jalal DI, Smits G, Johnson RJ, Chonchol M. Increased fructose associates with elevated blood pressure. Journal of the American Society of Nephrology : JASN 2010;21:1543-9.

25. Gersch MS, Mu W, Cirillo P, et al. Fructose, but not dextrose, accelerates the progression of chronic kidney disease. Am J Physiol Renal Physiol 2007;293:F1256-61.

26. Vasdev S, Gill V, Parai S, Longerich L, Gadag V. Dietary vitamin E and C supplementation prevents fructose induced hypertension in rats. Mol Cell Biochem 2002;241:107-14.

27. Hu QH, Zhang X, Pan Y, Li YC, Kong LD. Allopurinol, quercetin and rutin ameliorate renal NLRP3 inflammasome activation and lipid accumulation in fructose-fed rats. Biochem Pharmacol 2012;84:113-25.

28. Johnson RJ, Nakagawa T, Sanchez-Lozada LG, et al. Umami: the taste that drives purine intake. J Rheumatol 2013;40:1794-6.

29. Sanchez-Lozada LG, Mu W, Roncal C, et al. Comparison of free fructose and glucose to sucrose in the ability to cause fatty liver. Eur J Nutr 2010;49:1-9.

30. Avena NM, Long KA, Hoebel BG. Sugar-dependent rats show enhanced responding for sugar after abstinence: evidence of a sugar deprivation effect. Physiol Behav 2005;84:359-62.

31. Hu FB, Malik VS. Sugar-sweetened beverages and risk of obesity and type 2 diabetes: epidemiologic evidence. Physiol Behav 2010;100:47-54.

32. Malik VS, Popkin BM, Bray GA, Despres JP, Willett WC, Hu FB. Sugar-sweetened beverages and risk of metabolic syndrome and type 2 diabetes: a meta-analysis. Diabetes Care 2010;33:2477-83.

33. Montonen J, Jarvinen R, Knekt P, Heliovaara M, Reunanen A. Consumption of sweetened beverages and intakes of fructose and glucose predict type 2 diabetes occurrence. J Nutr 2007;137:1447-54.

34. Odegaard AO, Koh WP, Arakawa K, Yu MC, Pereira MA. Soft drink and juice consumption and risk of physician-diagnosed incident type 2 diabetes: the Singapore Chinese Health Study. American journal of epidemiology 2010;171:701-8.

35. Palmer JR, Boggs DA, Krishnan S, Hu FB, Singer M, Rosenberg L. Sugar-sweetened beverages and incidence of type 2 diabetes mellitus in African American women.

Arch Intern Med 2008;168:1487-92.

36. Schulze MB, Manson JE, Ludwig DS, et al. Sugar-sweetened beverages, weight gain, and incidence of type 2 diabetes in young and middle-aged women. Jama 2004;292:927-34.

37. Johnson RJ, Segal MS, Sautin Y, et al. Potential role of sugar (fructose) in the epidemic of hypertension, obesity and the metabolic syndrome, diabetes, kidney disease, and cardiovascular disease. Am J Clin Nutr 2007;86:899-906.

38. Rubinstein H, Zimmet P. Phosphate, Wealth, and Health in Nauru: A Study of Lifestyle Change. Gundaroo: Brolga; 1993.

39. Roncal-Jimenez CA, Ishimoto T, Lanaspa MA, et al. Dehydration-Induced Renal Injury: A Fructokinase Mediated Disease? Kidney Int 2013;2013:in press.

40. Lanaspa MA, Ishimoto T, Li N, et al. Glucose-induced obesity, fatty liver and insulin resistance is mediated by endogenous fructose. Nature Commun 2013;in press.

41. Ishimoto T, Lanaspa MA, Rivard CJ, et al. High-fat and high-sucrose (western) diet induces steatohepatitis that is dependent on fructokinase. Hepatology 2013;58:1632-43.

42. Neel JV. Diabetes mellitus: a "thrifty" genotype rendered detrimental by "progress"? Am J Hum Genet 1962;14:353-62.

43. Johnson RJ, Lanaspa MA, Gaucher EA. Uric acid: a danger signal from the RNA world that may have a role in the epidemic of obesity, metabolic syndrome, and cardiorenal disease: evolutionary considerations. Semin Nephrol 2011;31:394-9.

44. Watanabe S, Kang DH, Feng L, et al. Uric acid, hominoid evolution, and the pathogenesis of salt-sensitivity. Hypertension 2002;40:355-60.

45. Johnson RJ, Andrews P. Fructose, Uricase, and the Back-to-Africa Hypothesis. Evol Anthropol 2010;19 250-7.

46. Oda M, Satta Y, Takenaka O, Takahata N. Loss of urate oxidase activity in hominoids and its evolutionary implications. Mol Biol Evol 2002;19:640-53.

47. Keebaugh AC, Thomas JW. The evolutionary fate of the genes encoding the purine catabolic enzymes in hominoids, birds, and reptiles. Mol Biol Evol 2010;27:1359-69.

48. Tapia E, Cristobal M, Garcia-Arroyo FE, et al. Synergistic effect of uricase blockade plus physiological amounts of fructose-glucose on glomerular hypertension and oxidative stress in rats. Am J Physiol Renal Physiol 2013;304:F727-36.

49. Kratzer JT, Lanaspa MA, Murphy MN, et al. Evolutionary history and metabolic insights of ancient mammalian uricases. Proceedings of the National Academy of Sciences of the United States of America 2014;111:3763-8.

50. Friedlaender JS, Friedlaender FR, Reed FA, et al. The genetic structure of Pacific Islanders. PLoS genetics 2008;4:e19.

51. Kayser M, Brauer S, Cordaux R, et al. Melanesian and Asian origins of Polynesians: mtDNA and Y chromosome gradients across the Pacific. Mol Biol Evol 2006;23:2234-44.

52. Zimmet PZ, Whitehouse S, Jackson L, Thoma K. High prevalence of hyperuricaemia and gout in an urbanised Micronesian population. Br Med J 1978;1:1237-9.

53. Lennane GA, Rose BS, Isdale IC. Gout in the Maori. Ann Rheum Dis 1960;19:120-5.

54. Cheng LS, Chiang SL, Tu HP, et al. Genomewide scan for gout in taiwanese aborigines reveals linkage to chromosome 4q25. Am J Hum Genet 2004;75:498-503.

55. Ho CS, Tsai AC. Prevalence of overweight and obesity and its associated factors in aboriginal Taiwanese: findings from the 2001 National Health Interview Survey in Taiwan. Asia Pac J Clin Nutr 2007;16:572-9.

56. Prior IA, Rose BS, Davidson F. Metabolic Maladies in New Zealand Maoris. Br Med J 1964;1:1065-9.

57. Evans JG, Prior IA, Harvey HP. Relation of serum uric acid to body bulk, haemoglobin, and alcohol intake in two South Pacific Polynesian populations. Ann Rheum Dis 1968;27:319-25.

58. Gosling AL, Matisoo-Smith E, Merriman TR. Gout in Maori. Rheumatology (Oxford) 2013.

59. Johnson RJ, Titte S, Cade JR, Rideout BA, Oliver WJ. Uric acid, evolution and primitive cultures. Semin Nephrol 2005;25:3-8.

60. Prior IA, Rose BS, Harvey HP, Davidson F. Hyperuricaemia, gout, and diabetic abnormality in Polynesian people. Lancet 1966;1:333-8.

61. Buckley H, Tayles N, Halcrow SE, Robb K, Fyfe R. The people of Wairau Bar: a re-examination. J Pac Archaeol 2010;1:1-20.

62. Buckley HR. Epidemiology of gout. Perspectives from the past. Current Rheum Reviews 2011;7:106-13.

63. Buckley HR. Possible gouty arthritis in Lapita-associated skeletons from Teouma, Efate Island, Central Vanuatu. Current Anthropology 2007;48:741-9.

64. Rothschild BM, Heathcote GM. Characterization of gout in a skeletal population sample: presumptive diagnosis in a Micronesian population. Am J Phys Anthropol 1995;98:519-25.

65. Prior IA, Welby TJ, Ostbye T, Salmond CE, Stokes YM. Migration and gout: the Tokelau Island migrant study. Br Med J (Clin Res Ed) 1987;295:457-61.

66. Rasheed H, Phipps-Green A, Topless R, et al. Association of the lipoprotein receptor-related protein 2 gene with gout and non-additive interaction with alcohol consumption. Arthritis research & therapy 2013;15:R177.

67. Hollis-Moffatt JE, Phipps-Green AJ, Chapman B, et al. The renal urate transporter SLC17A1 locus: confirmation of association with gout. Arthritis research & therapy 2012;14:R92.

68. Le MT, Lobmeyer MT, Campbell M, et al. Impact of genetic polymorphisms of SLC2A2, SLC2A5, and KHK on metabolic phenotypes in hypertensive individuals. PloS one 2013;8:e52062.

69. Chaves FJ, Corella D, Blesa S, et al. Xanthine oxidoreductase polymorphisms: influence in blood pressure and oxidative stress levels. Pharmacogenet Genomics 2007;17:589-96.

70. Parsa A, Brown E, Weir MR, et al. Genotype-based changes in serum uric acid affect blood pressure. Kidney Int 2012;81:502-7.

71. Shafiu M, Johnson RJ, Turner ST, et al. Urate Transporter Gene SLC22A12 Polymorphisms Associated with Obesity and Metabolic Syndrome in Caucasians with Hypertension. Kidney Blood Press Res 2012;35:477-82.

72. So WY, Wang Y, Ng MC, et al. Aldose reductase genotypes and cardiorenal complications: an 8-year prospective analysis of 1,074 type 2 diabetic patients. Diabetes Care 2008;31:2148-53.

73. Feig DI, Madero M, Jalal DI, Sanchez-Lozada LG, Johnson RJ. Uric acid and the origins of hypertension. J Pediatr 2013;162:896-902.

74. Frisch RE. Critical fatness hypothesis. Am J Physiol 1997;273:E231-2.

75. Nissim I, Horyn O, Daikhin Y, et al. Down-regulation of hepatic urea synthesis by oxypurines: xanthine and uric acid inhibit N-acetylglutamate synthase. The Journal of biological chemistry 2011;286:22055-68.

76. Hill JO, Peters JC, Catenacci VA, Wyatt HR. International strategies to address obesity. Obes Rev 2008;9 Suppl 1:41-7.

77. Hollis-Moffatt JE, Xu X, Dalbeth N, et al. Role of the urate transporter SLC2A9 gene in susceptibility to gout in New Zealand Maori, Pacific Island, and Caucasian case-control sample sets. Arthritis Rheum 2009;60:3485-92.

78. Yang Q, Kottgen A, Dehghan A, et al. Multiple genetic loci influence serum urate levels and their relationship with gout and cardiovascular disease risk factors. Circ Cardiovasc Genet 2010;3:523-30.

79. Caulfield MJ, Munroe PB, O'Neill D, et al. SLC2A9 is a high-capacity urate transporter in humans. PLoS Med 2008;5:e197.

80. 80. Dinour D, Gray NK, Campbell S, et al. Homozygous SLC2A9 mutations cause severe renal hypouricemia. Journal of the American Society of Nephrology : JASN 2010;21:64-72.

81. Batt C, Phipps-Green AJ, Black MA, et al. Sugar-sweetened beverage consumption: a risk factor for prevalent gout with SLC2A9 genotype-specific effects on serum urate and risk of gout. Ann Rheum Dis 2013.

82. McGarvey ST, Forrest W, Weeks DE, et al. Human leptin locus (LEP) alleles and BMI in Samoans. Int J Obes Relat Metab Disord 2002;26:783-8.

83. Benton M, Macartney-Coxson D, Eccles D, Griffiths L, Chambers G, Lea R. Complete mitochondrial genome sequencing reveals novel haplotypes in a Polynesian population. PloS one 2012;7:e35026.

84. Bo S, Cavallo-Perin P, Gentile L, Repetti E, Pagano G. Hypouricemia and hyperuricemia in type 2 diabetes: two different phenotypes. Eur J Clin Invest 2001;31:318-21.

85. Tuomilehto J, Zimmet P, Wolf E, Taylor R, Ram P, King H. Plasma uric acid level and its association with diabetes mellitus and some biologic parameters in a biracial population of Fiji. American journal of epidemiology 1988;127:321-36.

86. Thow AM, Snowdon W. The effect of trade and trade policy on diet and health in the Pacific islands. In: Hawkes C, Blouin C, Spencer H, Drager N, Dube L, eds. Trade, Food, Diet and Health: Perspectives and Policy Options. Chichester, England: Blackwell Publications; 2010: pp. 147-68.

87. Thow AM, Heywood P, Schultz J, Quested C, Jan S, Colagiuri S. Trade and the nutrition transition: strengthening policy for health in the Pacific. Ecol Food Nutr 2011;50:18-42.

88. Edwardes B, Frizelle F. Globalisation and its impact on the South Pacific. N Z Med J 2009;122:10-3.

89. Working Party adopts Samoa's membership 2011. (Accessed 28 October, 2011, at http://www.wto.org/english/news_e/news11_e/acc_wsm_28oct11_e.htm.)

90. Dunford E, Webster J, Metzler AB, et al. International collaborative project to compare and monitor the nutritional composition of processed foods. Eur J Prev Cardiol 2012;19:1326-32.

91. Marks K. Pacific islanders' fatal diet blamed on Kiwi exports. . The Independent 2002.

92. Cumming G. New Zealand officials are under pressure for placing trade in unhealthy meat cuts ahead of the health of Pacific Island nations. . New Zealand Herald 2010.

93. Statistics New Zealand and Ministry of Pacific Island Affairs (2010). . Demographics of New Zealand's Pacific population. Wellington2010.

94. Costello EJ, Keeler GP, Angold A. Poverty, race/ethnicity, and psychiatric disorder: a study of rural children. Am J Public Health 2001;91:1494-8.

95. Johnson RK, Appel LJ, Brands M, et al. Dietary sugars intake and cardiovascular health: a scientific statement from the American Heart Association. Circulation 2009;120:1011-20.