Effects of lifestyle interventions on inflammatory markers in the metabolic syndrome

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1. ABSTRACT

Metabolic syndrome (MetS) is a clustering of cardiovascular risk factors which places individuals at increased risk for cardiovascular morbidity and mortality. In addition to obesity and insulin resistance, inflammation is emerging as a potential etiologic factor of the syndrome. One hypothesis suggests that obesity contributes to insulin resistance through increased production of adipose-derived inflammatory cytokines. Currently, lifestyle change is the first line of treatment for MetS. Only recently, however, have studies begun exploring the effect of lifestyle interventions on the mediation of inflammation in individuals with MetS. This review summarizes the strongest evidence (i.e. randomized controlled trial data) for a role of lifestyle interventions (diet and/or exercise) on the improvement of inflammatory biomarkers in people with MetS. Of six studies assessed, lifestyle interventions were consistently successful at improving the inflammatory and metabolic profiles. Interestingly, improvements in the inflammatory profile were found to be largely independent of obesity. Data currently suggest that alterations in dietary composition may be the most effective lifestyle change, although there is a need for more research in this area.

2. INTRODUCTION

2.1. Metabolic syndrome: definition, prevalence, and risk

First recognized in 1988 (1), the metabolic syndrome (MetS) is a clustering of cardiovascular risk factors, including abdominal obesity, dyslipidemia, hypertension, and impaired glucose tolerance. Although varying definitions of the condition have been proposed by several organizations (2-6), distinguishing criteria are comparable, and in most cases diagnosis is contingent on the presence of at least three components. (The notable exception being the definition put forth by The American Association of Clinical Endocrinologists (AACE) in 2003, where diagnosis is ultimately left to clinical judgment (5).) Table 1 provides a chronological summary of the existing definitions of MetS, proposed by the European Group for the Study of Insulin Resistance (EGIR), World Health Organization (WHO), National Cholesterol Education Program (NCEP), AACE, and International Diabetes Federation (IDF). Of note, both the EGIR and the WHO definitions require the presence of insulin resistance for diagnosis of MetS (2, 3), while the IDF includes ethnic-specific abdominal obesity in their operational definition

Table 1. Proposed working definitions of MetS

Risk Factor	EGIR (1999)(2)	WHO (1999)(3)	NCEP ATP III (2002)(4)	AACE (2003)(5)[1]	IDF (2006)(6)
Obesity	Waist Circumference: - Men greater than or equal to 94 cm -Women greater than or equal to 80 cm	WHR: -Men greater than 0.90 -Women greater than 0.85 and/or BMI greater than 30 kg/m^2	Waist circumference: -Men greater than 102 cm -Women greater than 88 cm	BMI greater than or equal to 25 kg/m^2	[2]Central obesity (defined using waist circumference with ethnicity specific values) and/or BMI greater than 30 kg/m^2
Blood Pressure[3]	BP greater than or equal to 140/90 mmHg	BP greater than or equal to 140/90 mmHg	BP greater than or equal to 130/85 mmHg	BP greater than or equal to 130/85 mm Hg	BP greater than 130/85 mmHg
Cholesterol[3]	TG greater than or equal to 2.0 mmol/L	TG greater than or equal to 150 mg/dL	TG greater than or equal to 150 mg/dL	TG greater than or equal to 150 mg/dL	TG greater than 150 mg/dL
	HDL-C less than 1.0 mmol/L	HDL: -Men less than 35 mg/dL -Women less than 39 mg/dL	HDL: -Men less than 40 mg/dL -Women less than 50 mg/dL	HDL: -Men less than 40 mg/dL -Women less than 50 mg/dL	HDL: -Men less than 40 mg/dL -Women less than 50 mg/dL
Blood Sugar[3]	FPG greater than or equal to 6.1 mmol/L [2]Insulin resistance defined as the top 25% of the fasting insulin values among non-diabetic individuals	[2]Presence of Type 2 diabetes, impaired glucose tolerance, impaired fasting glucose or insulin resistance	FPG greater than or equal to110 mg/dL	FPG = 110-126 mg/dL, or 2-hour post glucose challenge greater than140 mgldL	FPG greater than 100 mg/dL, or previously diagnosed Type 2 diabetes
Other		Microalbuminuria: urinary albumin excretion ratio greater than or equal to 20 mg/min or albumin : creatinine ratio greater than or equal to 30 mg/g		Family history or high risk of Type 2 diabetes, hypertension, or CVD, PCOS, old age, sedentary lifestyle	

[1]Diagnosis depends on clinical judgment based on risk factors.[2]Indicates that risk factor must be present for diagnosis to be made [3]Use of medication to control this condition is considered diagnostic. Abbreviations: BMI = body mass index, BP = blood pressure, cm = centimeter, CVD = cardiovascular disease, dL = deciliter, EGIR = European Group for the Study of Insulin Resistance, FPG= fasting plasma glucose, g = gram, HDL-C = high density lipoprotein cholesterol, IDF = International Diabetes Federation, kg = kilogram, L = liter, m = meter, min = minute, mmHg = millimeters mercury, mmol = millimole, NCEP ATP III = National Cholesterol Education Program Adult Treatment Panel III, PCOS = poly cystic ovary syndrome, TG = triglyceride, WHO = World Health Organization, WHR = waist to hip ratio

(6). Although subtle, varying emphases of select clinical criteria reveal fundamental differences in organizational views of the etiologic nature of the disorder. Presently, the NCEP characterization is the most widely used as a working definition for research (7), although to strengthen cross-study comparisons, there is a clear need for a univocal definition of the disorder.

MetS (as categorized by NCEP criteria) is thought to affect as many as one in five United States adults. Although prevalence of the condition increases with age (8), data reveal younger generations are also at risk (9). While the clinical utility of this condition has been questioned (10), several recent studies confirm higher cardiovascular disease (CVD) risk in individuals with three or more MetS components compared to individuals manifesting just one or two (11-16). Further, individuals exhibiting MetS have an increased risk of cardiovascular (hazard ratio (HR): 95% confidence interval (CI)): 2.26: 1.61-3.17)) and all-cause (1.44: 1.17-1.84)) mortality compared to healthy counterparts (14). People with MetS also have a five-fold greater risk of developing diabetes mellitus (DM), if not already present, than those without (17). Finally, recent epidemiologic evidence also suggests that MetS may be a risk factor for the onset of aging-related disability (18, 19), although future research in this area is needed before definitive conclusions can be drawn. Given the prevalence of MetS and its contribution to increased morbidity and mortality, an understanding of its etiology and through it a rational approach to its therapy is of considerable public health concern.

2.2. Potential etiologic factors of metabolic syndrome

While characterization of the underlying cause(s) of MetS is still the subject of debate, obesity and disorders of adipose tissue, and insulin resistance have emerged as potential etiologic factors. In support of this, several observational studies identify obesity (20-22) as an independent predictor of MetS. Furthermore, adiposity plays a key role in the pathophysiology of all MetS components (23-25), and is associated with insulin resistance (26). Despite this association, it should be noted that insulin resistance can occur at any given level of body fat (27). And, insulin resistance, independent of obesity, can influence several MetS components (28-30), leading some investigators to place a greater priority on insulin resistance than obesity in the pathogenesis of the syndrome (2, 3, 31).

One hypothesis which attempts to unify these factors suggests that obesity contributes to insulin resistance through an increased production of adipose-derived inflammatory cytokines (or "adipokines"). Cytokines, most commonly interleukins (ILs), are regulatory proteins typically released by cells of the immune system that act as intercellular mediators in the

generation of an immune response. However, several cytokines are also secreted from adipose tissue (32), especially visceral fat depots (33), and excessive fat accumulation can induce a pro-inflammatory state. While acute inflammation is a necessary response of the immune system, prolonged inflammation, even a low-grade state, has detrimental health effects (34-36). Weight loss reduces inflammation, and several studies consistently show that the magnitude of decrease in inflammatory markers is linearly related to the amount of fat lost (37-39). Interestingly, recent data suggest that regional fat distribution, independent of obesity, is associated with MetS. In a 2005 cross-sectional study, Health Aging, and Body Composition (Health ABC) investigators found visceral fat accumulation to be independently associated with MetS in older men and women, even in those of normal weight (odds ratio (OR), 95% CI men: 2.1, 1.6-2.9; women: 2.3, 1.6-3.5) (25). Surprisingly, these associations were much less robust or even nonexistent for subcutaneous adipose tissue, implying that properties of visceral adipose tissue itself, such as the secretion of adipokines, are associated with, and may even cause (40), MetS.

Perhaps the most compelling evidence substantiating the hypothesis of a direct role for inflammation in obesity-linked insulin resistance comes from a 1993 mouse model by Hotamisligil *et al.* (41). In this seminal study, authors showed that the inflammatory cytokine tumor necrosis factor alpha (TNF-alpha) is elevated in plasma and in adipose tissue of obese rodents, and that the neutralization of TNF-alpha (by soluble TNF-alpha receptor) leads to a significant decrease in insulin resistance in these animals. These data clearly point to a direct role of TNF-alpha in obesity-linked insulin resistance; a finding which has subsequently been replicated in humans (42). Since then, several studies have confirmed increased plasma concentrations of inflammatory cytokines in obesity (43-45), as well as insulin resistance (46, 47). Thus, several lines of evidence suggest that the two most prominent components of MetS, adiposity and insulin resistance, are associated with inflammation. Therefore, inflammation may be an underlying cause of MetS.

2.3. Inflammation and metabolic syndrome

The first study to specifically observe an association between inflammatory biomarkers (i.e. C-reactive protein (CRP), fibrinogen, white cell count) and various components of MetS was conducted by Festa in 2000 (48). Utilizing data from the Insulin Resistance Atherosclerosis Study (IRAS), authors found higher CRP levels in those with a greater number of metabolic disorders.(48) Since then, several studies have corroborated this finding (49-51), even in individuals without overt CVD or DM (52, 53). In addition to CRP, elevations in IL-6, IL-18, and TNF-alpha are correlated with the presence of MetS (54, 55); while adiponectin, an anti-inflammatory protein, has a negative association with MetS (54). Interestingly, these associations can be found at all levels of adiposity (56, 57). Data also show concurrent changes in systemic inflammation and the progression of

MetS. Similar to the findings by Festa *et al.* (48) in 2003, Ridker reported that over an eight year period, median CRP levels increased in response to the severity of MetS (number of markers) in 14,719 participants of the Women's Health Study (52). Results from this study further indicate that MetS and inflammatory processes are related.

Evidence also exists in support of a causal role of inflammation in the development and progression of MetS. In a six-year prospective study of 1244 Mexican adults initially free of diabetes, women in the highest tertile of CRP (greater than 2.17 mg/L) at baseline had an increased relative risk of developing MetS by 4.0 (95% CI: 2.0–7.9) compared with women in the lowest tertile (less than 1.24 mg/L) (58). This result was not observed for men (58); however, in a prospective study of similar design, significant predictive ability of CRP for MetS was seen in both genders (59). In this Italian cohort of healthy men and women (n=1658), higher baseline CRP values was found to confer a significant increased risk of developing MetS, independent of weight gain. Specifically, baseline CRP values greater than 2.1 mg/L had an 86% (95% CI: 81-90) sensitivity and 75% (69-81) specificity in predicting future MetS (59). In addition to CRP, hyperfibrinogenemia (representative of an inflammatory state) predicts MetS in men (60). Although inflammatory biomarkers are not yet considered to be diagnostic criteria of MetS, the recent IDF consensus recommends that additional research be conducted to elucidate the role of elevated circulating inflammatory and/or thrombotic markers or reduced levels of anti-inflammatory molecules in the development of MetS (6).

In addition to data implicating inflammation in the incidence and prevalence of MetS, recent evidence is suggestive of an additive effect of MetS and inflammation, specifically CRP, on CVD risk prediction. Two recent studies found that the age-adjusted relative risk of incident CVD events was the same in subjects with high CRP without MetS and in subjects with low CRP with MetS; however, in subjects with both elevated CRP levels and the presence of the MetS, the relative risk of CVD events was double that of the other subgroups (61, 62). Thus, reduction of inflammation in subjects with MetS may also improve risk for CVD. Therefore, the inflammatory cascade could be a critical therapeutic target for people with MetS.

3. LIFESTYLE INTERVENTIONS AND METABOLIC SYNDROME

The primary management of MetS involves healthy lifestyle promotion through caloric restriction, increased physical activity, and improved dietary composition (63). Such intervention strategies have been shown to reduce the prevalence of MetS by 40-80% (64-67), and may also favorably affect inflammatory profiles. Weight loss is associated with reductions in inflammatory biomarkers (38). Further, data from randomized controlled trials (RCTs) indicates that aerobic exercise can also reduce inflammation, especially when conducted in "inflamed" individuals, or if the exercise results in weight loss (68).

Table 2. Descriptive characteristics of randomized controlled trials examining the effect of exercise and weight loss on markers of systemic inflammation in subjects with MetS

Reference	Duration (mo)	N(M:F)/age (years)	Intervention/Description	Improvement in MetS Components?	Inflammatory Biomarkers	Change in Biomarkers?
65	24	90(49:41)/44.3+/-6.4	Mediterranean Diet	Yes	CRP, IL-6, IL-7, IL-18	↓ in all biomarkers for diet group
		90(50:40)/43.5+/-5.9	Control			
78	3	9(9:0)/45(41-59)	Pravastatin + 45-60 min aerobic + resistance activity 3 times/wk	Yes	MCP-1, IL-8	↓ IL-8 and ↓ MCP-1 in exercise groups
		9(9:0)/42(40-52)	45-60 min aerobic + resistance activity 3 times/wk			
		8(8:0)/55(47-62)	Pravastatin			
		6(6:0)/46(44-45)	Control			
77	3	9(9:0)/45(41-59)	Pravastatin + 45-60 min aerobic + resistance activity 3 times/wk	Yes	E-selectin, ICAM-1, VCAM-1, TNF-alpha, Adiponectin	↓ TNF-alpha in exercise groups
		9(9:0)/42(40-52)	45-60 min aerobic + resistance activity 3 times/wk			
		8(8:0)/55(47-62)	Pravastatin			
		6(6:0)/46(44-45)	Control			
75	12	169(70:99)/55.7+/-5.7	Lifestyle Changes (Diet + Exercise)	Yes	CRP, UA	↓ in CRP and UA in lifestyle intervention group
		166(70:96)/55.7+/-5.6	Control			
76	12	32(0:32)/68.7+/-3.4	20-60 min of endurance + resistance exercise 4 times/wk	Yes	CRP	↓ in CRP in exercise group
		33(0:33)/69.5+/-4.3	Control			
79	12	26(14:12)/ M: 49.0+/-8.8[1] F:57.6+/-6.0	LF diet + 45-60 min aerobic activity @ 60-85% HR_{max} 3 times/wk	Yes[2]	CRP	↓ in CRP for women in diet groups

[1]Age provided for entire cohort (n=274); results specific to those with MetS. [2]Only changes in cholesterol were reported, with a decrease in LDL in the treatment groups compared to control. Abbreviations: ↓ = decrease, CRP = C-reactive protein, ICAM-1 = intercellular adhesion molecule 1, IL = interleukin, LF = low fat, MCP-1 = monocyte chemotactic protein-1, Mets = metabolic syndrome, min = minute, mo = month, TNF-alpha = tumor necrosis factor-alpha, UA = uric acid, VCAM-1 = vascular cellular adhesion molecule-1, wk = week

Finally, certain foods are known to exhibit anti-inflammatory properties (69-71), and this too may influence the circulating levels of inflammatory biomarkers, independent of weight loss. Given the importance of lifestyle changes in the mediation of MetS, and the emerging role of inflammation in the characterization of the disorder, this section will summarize the strongest evidence (i.e. RCT data) for a role of lifestyle interventions on the improvement of inflammatory biomarkers in people with MetS. We acknowledge that additional lifestyle based interventions, such as smoking cessation and stress management, may be beneficial for the improvement of inflammatory parameters and MetS (72-74), but for the purpose of this review, lifestyle based interventions will be limited to diet and/or exercise trials.

3.1. Literature search and trial descriptions

A comprehensive literature search was conducted using the PUBMED database (National Library of Medicine, Bethesda, MD) inclusively through March 31, 2010 on RCTs using the keywords: metabolic syndrome, lifestyle intervention, inflammation, cytokine, exercise, nutrition, and diet. Relevant study details are presented in Table 2. Briefly, a total of six studies were identified which specifically examined the effects of diet and/or exercise interventions to improve inflammatory markers in subjects with MetS: three were exercise-only, two diet and exercise, and one diet-only. Study sample sizes ranged

from 32 to 335 individuals, and intervention duration ranged from 3 to 24 months. CRP was the most commonly measured inflammatory biomarker and in most cases the lifestyle intervention improved both inflammatory and metabolic profiles.

One of the earliest trials examined the effects of dietary composition on inflammatory biomarkers in men and women with MetS (65). Specifically, 180 Italians with MetS were randomized to follow either a Mediterranean-style (n=90) or control diet (n=90) for two years. Although both diets were similar in macronutrient breakdown (carbohydrate=50-60%, protein=15-20%, less than 30% fat), the Mediterranean-style diet emphasized the consumption of fruits, vegetables, nuts, olive oil and whole grains, whereas the control diet had no specific "food" emphasis. Endothelial dysfunction and markers of vascular inflammation (CRP, IL-6, IL-18) were primary study endpoints. Upon study completion, patients on the Mediterranean diet lost more weight than the control group and had lower plasma levels of CRP and IL-6, as well as less insulin resistance. Improvements in the inflammatory profile persisted even after controlling for weight loss. Additionally, participants on the Mediterranean diet reduced total cholesterol and triglycerides and increased their high density lipoprotein cholesterol (HDL-C) over the course of the study significantly more than participants on the control diet. Remarkably, after two years only 40 out

of 90 patients on the Mediterranean diet still had features of MetS, compared with 78 of 90 on the control diet.(65) Results from this study suggest that dietary composition, beyond weight loss, may be a salient intervention component. Bo *et al.* (75) evaluated the effects of individualized caloric restriction and moderate-intensity exercise on metabolic variables and CRP and uric acid (UA) values in the experimental and control arms of a twelve-month randomized lifestyle intervention trial performed in patients with multiple metabolic abnormalities. This lifestyle-based intervention induced a modest reduction in body mass index (BMI) and waist circumference and substantial improvement in the prevalence of MetS and its components (31% absolute risk reduction). Moreover, the combined lifestyle intervention and resulted in significant reductions in CRP and UA (23% and 6.5%, respectively), when compared to control (75). Interestingly, similar to the findings of Esposito and colleagues (65), the significant improvement in CRP was noted even after adjustment for weight and waist modifications.

Pertaining to the mediating effects of exercise alone, one year of endurance and resistance training (20-60 minutes/day, four days/week) improved a variety of MetS criteria in older women with MetS, in addition to a 29% reduction in CRP levels (-0.68+/-1.80 mg/L) (76). Additionally, two studies conducted by Troseid *et al.* examined the effects of physical exercise and the HMG-CoA reductase inhibitor, pravastatin, on peripheral markers of inflammation (monocyte chemotactic protein-1 (MCP-1), IL-8, TNF-alpha, adiponectin, and cellular adhesion molecules (CAMs)) in patients with MetS (77, 78). No significant effects of the intervention were observed on CAMs or adiponectin; however, a significant reduction in TNF-alpha, MCP-1 and IL-8 was seen in the exercise groups (i.e. exercise alone, exercise plus pravastatin) compared to the non-exercise groups (pravastatin and control). Authors also showed that reductions in MCP-1 and IL-8 were correlated with reductions in visceral fat (r=0.41 and 0.28 for MCP-1 and IL-8, respectively); however, visceral fat did not decrease significantly in the exercise groups raising concern over whether or not these exercise-induced improvements can be considered independent of fat loss (78). Changes in TNF-alpha, however, were correlated with BMI (r=0.36) and waist circumference (r=0.42), and all were significantly improved with exercise (77).

Based on the results from the aforementioned studies, it appears that both diet and physical activity interventions are successful at improving both metabolic and inflammatory parameters in subjects with MetS. However, whether and to what degree one lifestyle factor is more important in promoting benefit, especially independent of weight loss, is largely unknown. The only RCT attempting to address this question was conducted by Camhi *et al.* in 2010 (79). This systematic comparison of the independent and combined effects of diet and exercise on CRP involved 47 men and 39 postmenopausal women with MetS, randomized into a one-year weight stable trial with four treatment groups: control, low-fat (LF) diet,

exercise or LF diet plus exercise. Women randomized to LF diet or LF diet plus exercise had greater reductions in CRP compared with both the control and exercise group (p=0.001). However, similar results were not observed for men. These results agree with the previously described RCTs in this review, suggesting that improvement in inflammatory markers can be seen independent of weight loss. Further, these results show that dietary composition, specifically a diet low in fat, is the most effective lifestyle factor in reducing inflammation (at least in women with MetS, and compared to exercise). Results from this study do agree with findings from a non-randomized clinical trial of similar design, where 36 months of diet (caloric and fat restriction) or diet plus exercise intervention caused significant weight reduction (change in BMI: -7.2+/-1.1, -6.6+/-1.5, and +0.4+/-1.3 kg/m^2, respectively) improvement in lipid and non-lipid abnormalities of MetS, and improvement in the inflammatory biomarker UA, compared to control (80). However, such indices were not different between intervention groups, reiterating that diet appears to be the most salient lifestyle component.

4.   DIET-RELATED   ANTI-INFLAMMATORY PROPERTIES

Food has both nutritive and functional value and, as evidenced by the Esposito (65) and Camhi (79) trials, changes in dietary composition may contribute additive benefits beyond weight loss for the management of inflammation in MetS. In both of these studies, authors speculate that increased consumption of vitamins, antioxidants and fibers may have influenced the cytokine milieu. Biologically, there is a basis for this proposition as fruits and vegetables (found in high quantities in both Mediterranean and low-fat diets) have tremendous antioxidant potential (81, 82), and several studies have found inverse associations between high fruit and vegetable consumption and inflammation and oxidative stress (83-86). Further, folate, polyphenols, antioxidants (such as vitamin C and beta-carotene) and fiber, found in a variety of fruits and vegetables are also related to lower levels of inflammation and oxidative stress in adults (87-92). In addition to anti-oxidant properties, the lowered insulin response associated with LF diets may also decrease the levels circulating of inflammatory biomarkers by influencing adipocyte function (93). Lastly, dietary interventions may improve inflammation in individuals with MetS through improvements in insulin resistance. Diets high in fructose and saturated fats have been shown to predispose rats to hyperinsulinemia (94), whereas diets containing nuts (95), red wine (96), and omega-3 fatty acids (97) (all components of a Mediterranean diet) appear to be protective. Unfortunately, the role of insulin resistance on the inflammatory response was underexplored in the presented trials; although, this may be an interesting question for future trials to pursue. In sum, foods found within a Mediterranean and LF diet contain anti-inflammatory properties which may explain their effectiveness in reducing inflammation in MetS.

5. PERSPECTIVE

There are very few RCTs conducted to date examining the role of lifestyle interventions on

inflammatory markers in people with MetS. However, available evidence suggests that lifestyle interventions are effective at improving inflammatory and metabolic profiles these individuals. Moreover, of the therapeutic lifestyle factors, dietary composition appears to play the most important role. Interestingly, in nearly all RCTs, improvement in inflammatory biomarkers occurred independent of a change in weight, although it is questionable whether some studies were adequately powered to examine this outcome.

More long-term, adequately powered studies should be conducted to substantiate the observations presented in this review. Although all trials accounted for changes in body weight, changes in insulin resistance were not considered as a confounding factor. Given its potential role as a mediator in the relationship between inflammation and MetS, future studies should take this variable into account. Based on the findings of this review, future studies may also consider examining the effect of specific dietary components (i.e. total fat, saturated fat, cholesterol, fiber, or macronutrient intake) on the inflammatory profile in subjects with MetS.

6. ACKNOWLEDGMENTS

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Abbreviations: AACE = America association of clinical endocrinologists, BMI = body mass index, CAM = cellular adhesion molecule, CI = confidence interval, CRP = c-reactive protein, CVD = cardiovascular disease, DM = diabetes mellitus, EGIR = European group for the study of insulin resistance, HDL-C = high density lipoprotein cholesterol, HMG-CoA= 3-hydroxy-3-methylglutaryl-coenzyme A, HR = hazard ratio, IDF = international diabetes federation, IL = interleukin, kg = kilogram, L = liter, LF = low-fat, m = meter, MCP-1 = monocyte chemotactic protein-1, MetS = metabolic syndrome, mg = milligram, n = sample size, NCEP = national cholesterol education program, OR = odds ratio, RCT = randomized controlled trial, TNF-alpha = tumor necrosis factor-alpha , UA = uric acid, WHO = world health organization

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