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Adherence to antihypertensive medications: is prescribing the right pill enough?

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ABSTRACT

Significant progress has been made in the management of hypertension (HTN) in the last 60 years. A large number of antihypertensive drugs (AHD) is available for effective control of elevated blood pressure (BP) that were also shown to be beneficial in improving all-cause mortality and cardiovascular morbidity in hypertensive individuals. Despite these successes, rates of BP control and outcomes in hypertensive patients remain suboptimal. Therefore, the availability of effective drug therapy itself appears to be insufficient to guarantee desirable results. Adherence to antihypertensive medications is a crucial mediator of favorable outcomes in treating HTN, and non-adherence, in turn, halts BP control. In this review, we will summarize the available evidence on health-related impacts of adherence to AHD, methods for the evaluation of adherence and potential interventions aimed to improve adherence in hypertensive individuals.

Keywords: adherence, antihypertensive drugs, compliance

INTRODUCTION

According to the most recent National Health and Nutrition Examination Survey (NHANES) 2007–2010, one in three US adults aged 20 and over have blood pressure (BP) ≥140/90 mmHg making hypertension (HTN) the most common chronic medical problem [1]. HTN is associated with enormous economic and personal burden through increased risk of heart disease, stroke and kidney disease [2–4]. The treatment of HTN with antihypertensive drugs (AHD) has been unequivocally shown to positively impact patient-related outcomes leading to a 20–25% reduction in acute coronary syndrome, 30–35% reduction in stroke and 50% reduction in heart failure [5–7].

There are 15 different classes and 68 individual AHD available for the treatment of HTN [8]; however, only 52.5% of treated individuals were found to have controlled BP in NHANES 2007–2010 [1]. These rates of BP control are lower than those observed in randomized controlled trials (RCTs). For example, in the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) 68.2, 66.3 and 61.2% of patients in the chlorthalidone, amlodipine and lisinopril groups, respectively [9], and 75.4% patients in the Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial achieved a BP goal of <140/90 mmHg [10]. Due to the potential to further improve outcomes in hypertensive individuals by increasing rates of BP control [11], it is important to understand barriers in achieving optimal BP targets.

The first safe and well-tolerated AHD such as thiazide diuretics, reserpine and hydralazine were introduced in the late 1950s and the first RCT of BP lowering (the Veterans Administration Cooperative Study Group on Antihypertensive Agents) unequivocally demonstrated cardiovascular benefits of treating HTN in 1967 [12, 13]. The importance of adherence to AHD was recognized shortly thereafter. In 1973, Blackwell wrote: 'MUCH time, effort and expense is spent in the study of the effects of drugs, but little attention is devoted to whether or not patients take them as directed. And yet the drug defaulter is part of every practice, and to prescribe effectively, physicians should know how to recognize and reduce factors that contribute to poor compliance' [14]. Adherence to medical treatment is an essential mediator of antihypertensive treatment, and, in turn, non-adherence is a crucial barrier to successful BP reduction [15, 16].

DEFINITION OF ADHERENCE

Historically, the first term used to describe behavior related to the following of medical professional advice was compliance

[17]. In 2003, the World Health Organization (WHO) advocated the term adherence—'active, voluntary, and collaborative involvement of the patient in mutually acceptable course of behavior to produce a therapeutic results' as a preferred term [18, 19]. In this definition, adherence describes all behaviors influencing patients' outcomes, such as medication-taking behavior, following dietary and lifestyle advice, vaccinations and keeping follow-up visits. Nonetheless, when medication-taking behavior is viewed separately, the terms *adherence* and *compliance* are actually used synonymously and describe 'the extent to which a patient acts in accordance with the prescribed interval, and dose of dosing regimen' and it is measured over time and reported as a percentage. The additional term *persistence* is applied to describe the duration of time from initiation to discontinuation of drug therapy [20–22]. Therefore, compliance (adherence) and persistence are two dimensions of medication-taking behavior.

Non-adherence can manifest in a variety of forms such as not following the prescribed medical plan in general or can be related to non-adherence with medications, diet, medical appointments or refusal to stop a dangerous habit (smoking, illicit drug or alcohol use). Qualitatively, non-adherence is any deviation from medical advice, and a dichotomous yes/no model can be applied to it. When adherence is assessed quantitatively, it is usually referred to medication-taking behavior [23], and the definition of non-adherence would vary with the specific condition. For example, different levels of adherence are expected to achieve the full protection offered by contraception drugs, antivirals for human immunodeficiency virus, versus statin therapy. With respect to AHD, there is a general agreement that compliance and persistence of >80% is considered to be 'good' adherence and <80% is 'poor adherence' [18]. These cutoffs were shown to discriminate outcomes in hypertensive patients and will be discussed below [24–27].

METHODS FOR ADHERENCE EVALUATION

The treatment of HTN requires a multifactorial approach including AHD and lifestyle modifications (diet, exercise, moderation of alcohol consumption, smoking cessation and weight control). However, there is a paucity of studies assessing adherence to lifestyle recommendations in hypertensive individuals [28–30], and the adherence to pharmacologic therapy has been the main focus of adherence research in HTN.

Figure 1 summarizes available methods for AHD adherence evaluation. In general, direct methods of adherence assessment are considered to be the most accurate [23]. At present, direct methods are not widely used in AHD adherence evaluation due to the high cost of measurement of drug or its metabolite levels, the lack of practicality of direct observation of patient taking AHD or the lack of validation in HTN of biomarker measurements. Nonetheless, the measurement of AHD metabolites may be helpful in some cases such as the evaluation of patients with resistant HTN or selection of patients for renal artery denervation [31].

Indirect methods for AHD adherence evaluation (Figure 1) have been vigorously explored, but the absence of gold standard method against which they could be compared has resulted in no accepted recommendations for their use as adherence assessment tools. Nevertheless, given the high prevalence of non-adherence to AHD in hypertensive adults, it is important for any health-care team caring for these patients to be familiar with, and to apply adherence evaluation methods as much as allowed by their available resources.

Self-administered questionnaires such as the Morisky Medication Adherence Scale-4 (MMAS-4) and Morisky Medication Adherence Scale-8 (MMAS-8) items have been validated in patients with HTN [32]. Both questionnaires are easy to administer and interpret and provide information for

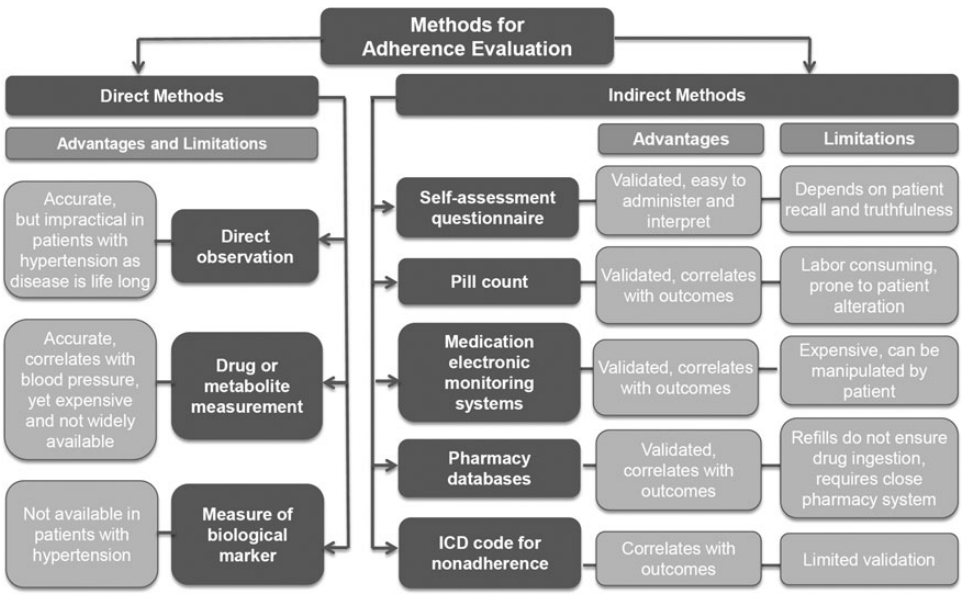

FIGURE 1: Methods for adherence evaluation.

possible interventions. In addition, adherence estimated from these scales was shown to correlate with results obtained by other methods (pill counts, pharmacy refills) and to correlate with BP control [33]. For example, the MMAS-4 has 4 'yes' or 'no' questions assessing different behavioral aspects such as forgetfulness, carelessness and possible side effects of AHD, with each question having a point value that determines the overall adherence score. MMAS-4 can be administered before provider visits and patients with low scores could be further targeted to improve medication adherence.

Pill counting (inspection of patients' medication containers) has been widely used in HTN adherence research due to the ease of administration and its objectivity [18]. The limitations of the pill count method include susceptibility to patient manipulation and provision of limited information about patterns of adherence [23]. Medication electronic monitoring system (MEMS) devices provide accurate information about adherence and allow the expansion of our understanding of different non-adherence patterns [34]. Electronic devices register each drug canister opening. In addition to information about the general frequency of medication use, it also allows analysis of timing, omission frequency and gaps in treatment. However, MEMS is not without limitations such as its high cost, lack of reimbursement by insurance companies and potential manipulation by patients (for example, the opening of the pill container may not ensure drug consumption). The Food and Drug Administration has approved a new ingestible event monitoring system, the Raisin™ Personal Monitor in 2010. This device avoids some of MEMS's limitations as it registers the actual act of pill swallowing by digestible sensors imbedded into pharmaceutical drugs that are activated by contact with gastric acid content and then transmit signals to a miniature monitor attached to the patient's skin. However, this 'smart pill' is not yet available for routine use.

The analysis of pharmacy dispensation records is also widely used in adherence research and expanded our knowledge about rates of medication non-adherence and its correlation with outcomes [18, 23]. Data obtained from pharmacy database analysis are easily quantifiable and objective; however, this method requires that patients use a closed pharmacy system. In addition, the medication dispensation does not ensure its consumption, nor does it provide information about the timing of taking the medications. Nevertheless, it is probably the most practical way to assess medication adherence, especially on large scales, and allows determination of two aspects of medication adherence, namely compliance and persistence. Compliance is usually assessed by using the methods of medication possession ratio (MPR) [35] and proportion of days covered (PDC) [36]. Both MPR and PDC are related to the number of available doses dispensed in relationship to the number of days during the observation period. The main difference between these two methods is that MPR can be numerically expressed as any number between 0 and >100% and can thus account for medication overfills (although it has been argued that MPR may overestimate overall medication adherence) [37]; while, in PDC the number of days covered by the drug cannot exceed a value of 100%. AHD persistence is determined by time (number of days expressed between 0 and 100%) from the initial drug prescription during which patient continues to refill his/her medication with allowed gaps between prescriptions. There is a substantial heterogeneity in methods that have been employed to describe AHD persistence calling for a need of standardization of this method in order to compare results obtained in different studies [38].

In the mid-1970s, the International Classification of Diseases 9th Edition (ICD-9) introduced a new code for medical non-adherence (V15.81), described as 'personal history presenting hazards to health and noncompliance with medical treatment'. The V15.81 code was intended to describe non-adherence with medications, refusal of medical procedures and non-adherence or inability to follow a medical plan or dietary recommendations. Although the V15.81 code was available for the last 30 years, there is a paucity of data about its validity. Recently, we evaluated the association between the V15.81 code and all-cause mortality in 18 822 newly diagnosed hypertensive US veterans and found that the presence of the V15.81 at the time of initiation of AHD strongly predicted higher all-cause mortality and, therefore, can be a useful tool in identifying high-risk hypertensive individuals [39]. However, the V15.81 code cannot be used to substitute the evaluation of AHD adherence, as we found a complex relationship between the V15.81 code and compliance to AHD as assessed by the PDC method. In newly diagnosed hypertensive individuals, a V15.81 code that was present at baseline (and thus determined by factors independent of future AHD use) predicted worse survival independently of AHD compliance. In contrast to this, in hypertensives who received a V15.81 code after the initiation of AHD, adjustment for AHD compliance attenuated the association between the V15.81 code and all-cause mortality. This highlights the potential heterogeneity of reasons that providers use to allocate a V15.81 code. The recognition of the complex nature of non-adherent behavior led to the substitution of a single V15.81 code by eight different non-adherence codes in the new *ICD-10* edition (Z91.11-Z91.19). It is desirable that providers and pharmacists include systematically the ICD non-adherence codes as a separate diagnosis of non-adherence. Additionally, more studies are needed to understand the utility of these codes in routine practice.

The achievement of BP control of <140/90 mmHg for the majority of hypertensive patients is the goal HTN therapy [3] and may be viewed as a surrogate of adherence. Studies consistently show that patients with better adherence to AHDs are more likely to have their BP under control [31, 33, 40]. Therefore, inadequately controlled office BP despite a reasonable number of prescribed AHDs (for example, a patient with Stage 1 HTN who has uncontrolled BP on 2–3 AHD) may be a clue for non-adherence. However, this approach has several caveats, such as office BP influence by 'white coat effect' when office BP is higher than BP observed in an ambulatory setting and 'white coat adherence'-improved adherence to AHDs around provider visit [41, 42]. Therefore, although overall helpful, BP values itself are not an adequate marker of adherence and, when non-adherence is suspected, it should be tested by additional methods such as patient questionnaires, pill counts or a review of AHD refill patterns.

Even in the absence of accepted widespread methods for non-adherence screening, it is important that providers routinely ask questions in a non-threatening manner to elicit possible problems with adherence. Simple questions such as 'do you ever forget to take your medications?' or 'when you feel better (worse) do you sometimes stop taking your medications?' can help identify patients with poor adherence [43]. In our opinion, it is also helpful to ask patients to bring all their medication bottles to the follow-up visits and routinely review refill dates and numbers of remaining pills—this only requires few extra minutes and can provide useful information about adherence. In addition, asking patients to maintain home BP diaries may improve awareness about BP control and adherence to AHD; although, studies are needed to support this recommendation.

NON-ADHERENCE TO AHD AND OUTCOMES

Non-adherence to AHD is very common [44] and is associated with worse BP control [40, 45]. Given the heterogeneity of methods used to assess adherence, variable 1-year compliance rates ranging from 20 to 80% were reported [40, 46–48]. Persistence usually declines over time and 42% of newly hypertensive patients were shown to stop their AHDs at 1 year after the start of the treatment.[49] Additionally, in a large European observational study with 10-year follow-up, it was found that each year ∼40% of patients were not taking their AHD [50]. It was also demonstrated by using MEMS that on any given day, 10% of hypertensive patients are omitting some doses of AHD [51]. Adherence rates may be higher to single-drug therapy with minimal number of doses per day [48] and to certain AHD classes, such as renin–angiotensin system blockers and calcium channel blockers, when compared with diuretics and β-blockers [46, 52–54]. The adherence to dietary recommendations is even lower than adherence to AHD. Galletti *et al.* reported that only 10 and 19% of men and women with HTN, respectively, were adherent to low sodium diet, and only 5–8% of these patients had an adequate potassium intake [55]. Similarly, 19% adherence rate to low sodium diet was reported by De Nicola *et al.* in patients with chronic kidney disease and HTN [56].

The analysis of adherence through pharmacy databases allows studying large groups of patients, and it has been the most commonly used tool to evaluate the relationship between AHD adherence and patient-related outcomes, such as all-cause mortality, cardiovascular morbidity, hospitalizations and end-stage kidney disease (ESKD). Across the board, the available literature uniformly shows an adverse association between poor adherence to AHD and health-related outcomes. In a study involving 31 306 newly treated hypertensives during a 4-year follow-up period, patients with excellent adherence (PDC >80%) had 63% reduced risk of all-cause mortality [hazard ratio (HR) 0.37, 95% CI 0.31–0.45] when compared with patients with low adherence (PDC <40%) [25]. While the above study did not find a reduced risk of stroke and acute myocardial infarction (AMI) in newly treated hypertensive patients with higher adherence, another study involving 77 173 prevalent hypertensives found that patients with lower persistence during 2 years of observation had subsequently a 15% higher risk of AMI [relative risk (RR) 1.15, 95% CI 1.00–1.33] and a 28% higher risk of stroke (RR 1.28, 95% CI 1.15–1.45) [24]. Similarly, Kettani *et al.* found that the incidence of cerebrovascular disease was 22% (RR 0.78, 95% CI 0.70–0.87) lower in incident hypertensive patients with good adherence (MPR ≥80%) when compared with lower adherence (MPR <80%) [26]. Additionally, Mazzaglia *et al.* also found that high adherence (PDC ≥80%) was associated with a 38% (HR 0.62, 95% CI 0.40–0.96) lower risk of a composite cardiovascular outcome (AMI, angina, stroke or transient ischemic attack) when compared with low adherence (PDC <40%) in newly treated hypertensives during 4.6 years of follow-up [57]. The dissimilarities on the impact of adherence to AHD and primary cardiovascular prevention by Esposti *et al.* [25] and other studies [24, 26, 57] could be related to differences in methodology used to evaluate the adherence, duration of follow-up and populations studied. A recent meta-analysis of 44 individual studies that included close to 2 million patients confirmed that good adherence to AHD (mostly assessed through analysis of pharmacy databases) was associated with 29% reduction in all-cause mortality (RR 0.71, 95% CI 0.64–0.78) and 19% reduction in the development of cardiovascular disease (RR 0.81, 95% CI 0.76–0.86) [58].

Elevated BP is a well-known risk factor for the development and progression of ESKD. Roy *et al.* analyzed the effect of adherence to AHD (via MPR) and the risk of development of ESKD in a large Canadian registry including 185 478 newly treated hypertensive patients aged 45–85 years. Patients with good adherence (MPR ≥80%) had 33% lower risk of ESKD during a mean follow-up of 5.1 yeas (HR 0.67, 95% CI 0.54–0.83) when compared with patients whose adherence was lower (MPR <80%) [27]. The healthy adherer effect (reduced risk of adverse outcome associated with adherence is a surrogate of overall healthy behavior rather than adherence to a specific drug) has been suggested as a concern regarding the interpretation of data about the impact of adherence to AHD on various outcomes. It has been shown in several RCTs that patients who were adherent to a placebo had better outcomes when compared with non-adherent patients in an active medication group [18]. Interestingly, Roy *et al.* looked at the association of adherence to other drugs (proton-pump inhibitors and benzodiazepines) and the associated risk of ESKD and found an unchanged risk of ESKD in patients with better compliance with these drugs, strengthening the notion that adherence to AHD is indeed protective of ESKD development rather than a surrogate marker of a healthy adherer effect [27].

The evaluation of adherence is especially important in patients with resistant HTN [59]. Non-adherence is a known cause of pseudoresistance and, if left undiagnosed, can lead to unnecessary diagnostic procedures and invasive treatments. Unappreciated non-adherence could be a potential reason for the success of renal artery denervation in general practice, while this procedure failed to show BP benefit over medical treatment in the setting of a carefully conducted RCT [60].

Table 1. Factors influencing adherence to AHD and the roles of provider in modifying these factors toward better patients' adherence

Factor	Examples	Role of provider in modifying the factor
Disease-related	HTN is a lifelong, mostly asymptomatic condition: patient has to weight future benefits with today's burden of treatment (cost, effort and side effects)	Educate patients about the benefits of controlling elevated BP in non-threatening manner and, where it is feasible, involve patients in the decision to treat elevated BP and in choosing medications
Patient-related	Physical factors Visual, hearing or cognitive impairment, immobility	Advise on how to use aids (medication containers that are prefilled by caregiver, specific treatment targeting disability when it is indicated)
	Psychosocial factors Poor knowledge about disease Cultural beliefs Poor understanding of why drugs are needed Fear of taking drugs and possible adverse effects Substance dependence	Educate and provide feedback about the harms of high BP and the benefits of treating elevated BP, discuss possible side effects of AHD and educate how to cope with them, reassure that medications can be changed if adverse effects arise. Provide a similar education for family members involved in patient's care when culturally appropriate Offer rehabilitation programs for substance dependence
Therapy-related	Complexity of drug regimen Duration of drug regimen (lifelong) Lack of immediate benefits of therapy Actual of perceived side effects Frequent changes in regimen	Simplify regimen, avoid drugs with multiple daily dosing, use long-acting drugs that 'allow' gaps in treatment Educate patient on the importance of the continuous need to take AHDs. Educate about potential side effects and create a plan of action Avoid undue frequent changes in the medication regimen
Socio-economic	Cost of treatment Health illiteracy Lack of health insurance Lack or limited access to providers Lack or limited access to pharmacy Unstable living conditions	Taylor medication regimen based on patients' insurance and income, offer manufacturers' discount coupons
Health-care system-related	Provider–patient relationship Provider communication skills Lack of positive reinforcement from provider Lack of provider's knowledge about adherence Restricted drug formularies and high co-pays Weak ability of system to educate patient and provide follow-up Poor access to providers and appointments	Be aware and continuously self-improve communication skills, encourage trust and communication Learn to listen, show empathy, offer praise for attaining treatment goals Be aware and learn about adherence rates and how to screen for non-adherence Be familiar with main insurance plans and medication coverages

CAUSES OF NON-ADHERENCE AND INTERVENTIONS TO IMPROVE ADHERENCE TO AHD

Traditional approaches evaluating the association between adherence and patient characteristics such as socio-demographic factors are falling out of favor due to the inconsistency of results across various studies (e.g. dissimilar associations between adherence and age and gender), and due to the non-modifiable nature of many 'traditional' patent characteristics (age, gender) [18, 23, 61]. Moreover, because HTN is a highly prevalent condition, it would be impractical to apply demographic and other traditional characteristics to a particular patient to assess whether he/she is at risk for non-adherence.

Although experts call medication non-adherence a diagnosable and treatable condition, [62] non-adherence cannot be cured by a 'magic pill'. Adherence to AHD is a behavior that is based on knowledge, perception and skills [63]; and it is influenced by multiple factors that WHO categorizes into five broad categories: patient-related, condition-related, therapy-related, socio-economic and health-care system related [19]. Table 1 lists the most common examples in each of these categories.

The majority of controlled interventions aimed to improve adherence to AHD-targeted patients and included education and behavioral support [64–78]. Few trials also involved interventions toward system delivery [64, 67, 70, 73, 79], provider education (mainly pharmacist rather than physicians) [67] and evaluation of collaborative care (physicians, pharmacists, social workers and nurses) [67, 75, 79]. A recent meta-analysis concluded that these interventions had overall low-to-moderate impact on AHD adherence [80]. Although many interventions moderately increased adherence with AHD, the increase in adherence to AHD was not always associated with a consistent improvement in BP control [68, 72, 74, 78], nor with the reduction in stroke, angina or myocardial infarction [78], or reduction in health-care utilization [72, 78].

In the absence of clear recommendations about the best intervention to improve adherence to AHD, the provider–patient relationship and the provider's role has been increasingly stressed as a vital part in the recognition and correction of non-adherence. Atreja *et al.* proposed the so-called SIMPLE method for providers treating patients with chronic conditions to improve medication adherence [43]. The SIMPLE mnemonic stands for Simplify regimen, Impart knowledge, Modify beliefs and behavior, Provide communication and trust, Leave the bias (tailoring communications based on cultural and social features) and Evaluate adherence. Table 1 shows areas where providers play key roles in improvement of adherence

to AHD. Notably, the SIMPLE method to enhance adherence is not so 'simple' in day-to-day practice as addressing non-adherence requires knowledge, time and practice. Therefore, continuous education of providers is important in dealing with non-adherence. In addition, the policy makers and insurance companies need to re-evaluate the approach to dealing with non-adherence and increase provider support, by, for example, providing routine reports based on pharmacy claims about patients' adherence. Increasing medication coverage and reduction in medication co-pays have been also shown to increase adherence to AHD [81, 82].

CONCLUSION

Adherence is a critical mediator between AHD and the reduction of complications associated with elevated BP. Non-adherence is extremely common and it is estimated to be present in almost one-half of patients with HTN. Poor adherence has been consistently shown to be associated with the worse survival, higher cardiovascular disease and ESKD in patients with HTN. Therefore, screening for non-adherence with AHD should be a part of routine care of hypertensive individuals. Unfortunately, no gold standard method that is easy to perform, inexpensive and acceptable to patients is available for non-adherence screening. It is important to involve policymakers and insurance companies in the development of programs to increase adherence. In the meantime, medical providers remain at the forefront in evaluating adherence and should have continuous education about non-adherence evaluation and follow the SIMPLE steps to enhance adherence with AHD.

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CONFLICT OF INTEREST STATEMENT

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FULL REVIEW

Obesity—a disease with many aetiologies disguised in the same oversized phenotype: has the overeating theory failed?

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ABSTRACT

Evolution has led to metabolic thrift in humans—a genetic heritage that, when exposed to the modern 'obesogenic' milieu with energy-dense food and a sedentary lifestyle, predisposes to obesity. The current paradigm that overeating of easily digestible carbohydrates and the resulting imbalance between energy in and out as the cause of overweight has recently been challenged. Indeed, studies suggest that the host response to various nutrients contributes to overeating and fat accumulation. Alterations in neurotransmitter functions, changes in the epigenome, dysbiosis of gut microbiota and effects of specific nutrients (or lack of such nutrients) on mitochondrial function and signalling pathways may promote fat accumulation independent of calories. Whereas nutrients that stimulate generation of uric acid (such as fructose and purine-rich food) cause insulin resistance and fat accumulation, other nutrients (such as antioxidants, plant food, probiotics, nuts, soy and omega-3) counteract the negative effects of a calorie-rich diet by salutary effects on mitochondrial biogenesis. Thus, the specific metabolic effects of different nutrients may be more important than its total energy content. By studying the impact of nutrients on mitochondrial health, as well as the trans-generational impact of nutrients during fetal life, and how specific bacterial species correlate with fat mass accumulation, new dietary targets for obesity management may emerge. Overeating and overshooting of calories could to a large extent represent a symptom rather than a cause of obesity; therefore, hypocaloric diets should probably not be the main, and certainly not the only, focus for treatment of the obese patient.

Keywords: epigenome, gut microbiota, insulin resistance, mitochondria, obesity

Saying that obesity is caused by eating too much is like saying that allergies are caused by breathing too much.—

Jonathan Bailor

INTRODUCTION

We experience a global pandemic of obesity and metabolic syndrome. This epidemic has important implications for both