Dysglycemia-Based Chronic Disease and Lifestyle Medicine: Mechanistic Interpretation Using the Allostatic Load Model

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Abstract.

Dysglycemia-based chronic disease (DBCD) comprises insulin resistance, prediabetes, and type 2 diabetes, and their staged progression, complications, and impact contribute to one of the largest public health burdens worldwide. The clinical and economic effects of DBCD are fueled by external stressors related to modern society and lifestyles, especially in low socioeconomic strata. Chronic stressor exposure leads to chronic stress, characterized by immune-neuroendocrine activation and mobilization/depletion of metabolic resources. This complex adaptive response engaging many different signaling pathways is termed allostasis and principally regulates homeostatic mechanisms. Allostatic load is the metabolic cost of adaptation to environmental factors and can lead to numerous adverse health outcomes and behaviors. In this narrative review, the bidirectional relationship between allostatic load and unhealthy behaviors is analyzed in the context of DBCD development and progression, with a focus to reduce individual vulnerabilities.

Key words

Dysglycemia; Diabetes; Lifestyle; Allostatic load

Introduction.

Diabetes represents one of the largest public health burdens worldwide.[1] In 2021, the global diabetes prevalence in adults was 10.5% (about 536.6 million people), similar between sexes, higher in older age, and higher in urban (12.1%) compared to rural (8.3%) areas (12.1% vs 8.3%).[2] To better expose opportunities to prevent development/progression of type 2 diabetes (T2D) and T2D complications, the Dysglycemia-Based Chronic Disease (DBCD) model has been devised. This complication-centric approach evolves through four distinct stages: Stage 1 – insulin resistance, when primary drivers (genetics, environment, and behavior fashion individual lifestyles and typically, abnormal adiposity); Stage 2 – prediabetes, when β-cell defects arise and mild hyperglycemia ensues; Stage 3 – T2D, when β-cell defects persist and worsen leading to moderate/severe hyperglycemia; and Stage 4 – complications, when macrovascular changes result from insulin resistance and microvascular changes result from hyperglycemia.[3]

Lifestyle medicine encompasses nonpharmacological and nonprocedural strategies in the management and prevention of chronic diseases. Lifestyle medicine interventions concentrate on primary drivers (genetics, environment, and behavior) and in the cardiometabolic space, on secondary metabolic drivers (adiposity, dysglycemia, hypertension, dyslipidemia, and residual factors [inflammation, malnutrition, thrombosis, etc.]).[4] In patients with DBCD, lifestyle medicine is primarily preventive and directed towards the earlier stages (1 and 2) by addressing modifiable health behaviors, however, also later DBCD stages would benefit from lifestyle interventions.[4]

Although a person's lifestyle and the accompanying behaviors can be interpreted as an individual characteristic, they are strongly determined by the external environment. For the most part, causes of DBCD are related to social and environmental stressors.[5,6,7] Chronic exposure to stressors leads to allostatic load (AL), which can be interpreted as a quantifiable, cumulative effect of stress responses.[8] Prolonged stress increases AL through the accrual of tissue injury and depletion of metabolic precursors, such as neurotransmitter precursor amino acids.[7,9] Conceptually, AL mediates the networking relationships of environmental stressors, lifestyle behaviors, and DBCD. The purpose of this narrative review is to parse out

these relationships to enrich our understanding of how lifestyle medicine can prevent DBCD development and progression.

1. Allostatic Load.

The notion of AL was introduced in 1993 by McEwen and Stellar.[8] The concept describes the cumulative impact of physiological stress, reflecting the level and nature of physiological adaptations to environmental change.[10] Homeostasis is the "resistance to change" and governs essential biological oscillators, which have a narrow target range. Allostasis is "stability through change," in which many different mechanistic pathways with a wide target range govern set-points for homeostasis. When the exposure to stressors is chronic or escalates, the cost of adaptation – allostatic load – rises, and if it exceeds the body's capacity, then a failure of allostatic mechanisms, or allostatic overload, results (Figure 1).[8,11] In effect, AL can be viewed as a driver of chronic disease, and in the context of immune-neuroendocrine axis activation that engenders insulin resistance, a driver of DBCD.[12]

Specifically, as part of the initial response to stressor exposure, cortisol, epinephrine, norepinephrine, and dehydroepiandrosterone sulfate are released and can be measured as primary biomarkers of AL.[8,11] Moreover, to compensate for any dysregulation of this adaptive response, secondary metabolic, inflammatory, and cardiovascular biomarkers appear.[11] In addition, numerous health conditions such as cardiovascular disease and mortality are considered as tertiary outcomes, but not generally part of an AL score.[8,11] Indeed, there is considerable methodological inconsistency among AL measurements, driven by the limited availability of commercially available primary biomarkers in epidemiological studies,[13] leading to variable reporting of AL scores based on different combinations of primary and secondary biomarkers.

2. Allostatic Load and Insulin Resistance.

Allostatic load has an impact on health and mortality,[10,14,15] as well as increased risk and prevalence of DBCD (Figure 2).[16,17] Several important consequences of AL are behavioral change, excessive calorie consumption, weight gain, and then abnormal adiposity distribution, a core component of the Adiposity-

Based Chronic Disease (ABCD) model that extends beyond body mass index (BMI) classifiers, and also includes the abnormal adipocyte secretome.[18,19] This pathophysiology continues with fatty acid/lipoprotein circulation exceeding the limited capacity of ectopic adipocytes to store lipid, causing fat deposition in ectopic sites.[19] The resulting dysfunctional adipose cells become inflamed (e.g., with abnormal macrophage activation and adipokine secretion) producing excessive free fatty acids and glycerol and eventually rendering an insulin resistant state (or DBCD Stage 1). Increased demands on insulin-producing pancreatic β-cells gradually impair insulin secretion and lead to hyperglycemia (DBCD Stages 2 and 3).[18]

3. Allostatic Load and Social Determinants.

The complex system of exposures acting on the background of the human genome is the exposome; this confers various risk determinants for cardiometabolic drivers, such as DBCD.[20] Specifical exposures can be physical (housing, working conditions, air pollution, and toxic environmental compounds [or disruptors], etc.) and nonphysical (economic, education level, crime/discrimination, food deserts/insecurity, etc.).[21] These social determinants of health (SDOH), and their causative structural determinants (e.g., policy and politics), predispose individuals to negative life events, lack of resources, life insecurity, limited access to health care, and risky work environment,[22] increasing risks for DBCD and overall poor health.[3,23]

People with lower socioeconomic positions generally present with increased AL,[13,24] in part explaining the associated increased DBCD risk. In one study from Poland[25] including 3,887 occupationally active men aged 25-60 years, there was a protective role of higher education level, being married, and residing in an urban area, each associated with lower AL.[25] Another study from the U.S.,[26] including 13,199 Caucasian, African American, and Mexican American men and women over age 20 years, it was found that those living in the more disadvantaged neighborhoods had higher AL compared to those living in the more favorable neighborhoods, with the greatest difference found in the African American population.[26] In The Korean Metabolic Syndrome Mortality Study of 70,713 middle-aged adults, socially disadvantaged groups presented with increased AL and an associated increased risk of premature death.[27] Additionally, AL seems to be a factor explaining racial disparities in mortality. In a previous study from the U.S. including 4,515 Caucasians and African Americans aged 35 to 64 years from the third NHANES study (1988–1994), African Americans had a greater social disadvantage and higher AL than Caucasians.[28]

Even though AL reflects long-term exposure to stress, it does not necessarily reflect current exposure to stress. In other words, the consequences of prior stressor exposures and AL can manifest at any time in one's life.[29] For example, the influence of the disadvantaged life environment during childhood can be observed later in life. This approach was investigated in a study of 1,008 adults from the U.S. where higher exposure to social stressors in childhood and earlier adulthood was associated with increased AL in late adulthood.[30] Previous studies also described, that cumulative stress is associated with accelerated biological aging.[31] Therefore, in the context of dysglycemia, having prior exposure to stressors any time earlier in the life can lead to DBCD development and progression.

4. Allostatic Load and Lifestyle.

Chronic stress can foment various risky behaviors, such as excessive risk-taking activities or unhealthy coping strategies. More specifically, these include substance abuse (alcohol consumption, cigarette smoking, drug use, etc.), eating disorders (overeating, anorexia nervosa, bulimia, etc.), sleep disturbances, and sedentary behavior. Those poor lifestyle choices are associated with AL, adverse cardiometabolic health, negative emotions, and behaviors, worsening of current chronic diseases, and development of new chronic diseases, all associated with some aspect of DBCD.[32]

4.1. Allostatic load and diet.

The role of lifestyle medicine in DBCD preventive care strategies emphasizes weight management and healthy dietary patterns.[4,33] Tactically, this includes not only reduction of excessive calories and incorporation of healthy foods (e.g., favorable molecular nutrition with high fiber, low glycemic index, plenty of plants, not skipping breakfast or night-binging, and avoidance of highly processed foods), but also consideration of the causes of unhealthy eating patterns.[34] Chronic stress increases cortisol secretion, enhances appetite, and is associated with food preferences high in sugar, sodium, and fat, while low in fiber and lean sources of protein[32]. Stress-induced unhealthy eating increases the risk of ABCD, DBCD, other metabolic drivers of cardiovascular disease, alterations in the gut microbiota, and low-grade systemic inflammation, in aggregate contributing to high AL.[32]

Another aspect related to unhealthy eating and excess weight is weight discrimination, which contributes to obesity stigmatization.[35] This stressor is highly prevalent among adults and children/adolescents and is associated with more than doubling the risk of having a high AL.[36] A significant relationship between food insecurity (lack of persistent access to a sufficient amount of healthy and safe food) and AL has also been reported.[32] Food insecurity is one of the SDOH that contributes to unhealthy eating. Negative effects connected to being overweight or food insecure are strongly associated with increased appetite, reinforcement of food-seeking behavior, consumption of bigger portions, and preference for less healthy food. This vicious cycle becomes hard to break, amplifying AL.[37]

4.2. Allostatic load and physical activity.

Physical activity is critical to a comprehensive lifestyle medicine preventive care plan for all stages of DBCD. Firstly, physical activity assists in weight management due to the increase in energy expenditure.[32] Secondly, physical activity has anxiolytic and antidepressant effects and can mitigate the harmful consequences of stress.[32] Additionally, physical activity has beneficial impact on circadian rhythm. Higher degrees of physical activity have been associated with cardiovascular conditioning and decreased oxidative stress, consequently lowering AL.[32] In a systematic review of 55 prospective studies, 76.4% indicated that psychological stress predicts less physical activity through behavioral inhibition.[38] However, 18.2% of studies indicated that psychological stress predicts more physical activity through behavioral activation.[38] In short, the relationship of stress, AL, and physical activity seems to be nonlinear and require further clarification in order to model this lifestyle medicine intervention more accurately.

4.3. Allostatic Load and Sleep Hygiene.

Sleep disturbances include abnormal amounts and circadian disruptions, and have been linked to hypothalamic dysfunction, hormonal changes, inflammation and cytokine effects, and insulin resistance.[39] Poor sleep hygiene is a predictor of high AL,[40] and high AL may be a driver of poor sleep.[41]. Newly arising sleep deprivation increases vulnerability to the effects of stress, contributing to this vicious cycle.[41]

4.4. Allostatic Load and Substance Abuse.

Tobacco smoking[42] and high alcohol consumption[43] increased the risk of dysglycemia. Individual abuses are closely related to stress exposure. An allostatic model of addiction, proposed in 2001,[44] partially explains brain changes in reward neurotransmission caused by abuses, involving compromised function in the dopamine and opioid peptide systems in specific components of the extended amygdala.[44] These brain changes lead to a high probability of relapses long after the abuses have ceased. Abuses downregulate reward systems in the brain, deviating considerably from the normal homeostatic point with each use, creating a persistent allostatic state that drives compulsive intake even further and, and in turn, increasing AL.[44] The majority of studies in diverse populations have shown that substance abuse is associated with higher AL.[32] However, few studies have shown the inverse association.[45,46] Contradicting results might be attributed to the strong influence of socioeconomic status on this association, as well as the varying influence of health risk behaviors on AL across the lifespan.[45,46] For instance, in a sample of rural African American youth,[45] individuals who made it to college and had lower substance use still had higher AL, compared to their peers who did not attend college. Similar results have also been found in a sample of indigenous Australian university students.[46] This peculiar association might be attributed to perceived discrimination in specific settings.

4.5. Causality between Allostatic load and Lifestyle

The causality and direction of the associations between AL and lifestyle has not been fully established. Two systematic reviews, including 10[7] and 26 studies,[32] investigated the association between AL and health risk behaviors. In general, both reviews confirmed the positive association between exposure to stressors and AL, but given that most of the studies were cross-sectional, causality could not be established. Even though placing health risk behaviors as predictors of high AL seems more intuitive than the inverse, the relationship between health risk behaviors and AL is complex and often bidirectional, creating a vicious cycle. Hence, more longitudinal studies are needed to understand the causality and directionality of these complex relationships.[7,32]

5. Linking Social Determinants of Health and Allostatic Load.

There are two possible mechanisms linking SDOH and AL: mediation and prediction. The first aspect represents the association between SDOH and AL, mediated by lifestyle, which further predicts DBCD risk. Individuals deal with stressful life by adopting unhealthy lifestyle behaviors, which lead to neuroendocrine and metabolic dysregulation in the body and then elevated AL. In a systematic review by Siew et al.,[22] most studies reported that the association between exposure to external stressors and the resulting AL can be partially explained by lifestyle behaviors. The spectrum of investigated lifestyle mediators is wide and differs among studies. Some studies focused on the assessment of selected behavioral factors separately. In a study of 1,008 U.S. men and women, the results identified tobacco smoking, frequency of fast-food consumption, and light alcohol consumption as contributory pathways accounting for the effects of lower socioeconomic positions on increased AL.[30] Another study from Scotland also found similar results.[47] In total, 999 participants aged approximately 35 years at the first data collection in 1987 were followed for 20 years. The study aimed to test the mediating role of psychological factors and health behaviors in the association between SDOH and AL. Among all behavioral factors, the only significant mediating effect was through tobacco smoking, which accounted for 33% attenuation.[47] The second potential mechanism describes AL driven by SDOH, as a predictor of an unhealthy lifestyle leading to increased DBCD risk. The physiological cost of adaptation is represented as AL and a direct consequence of chronic exposure to adverse SDOH. Accordingly, high AL then leads to unhealthy behaviors[32] and thereby increases the risk of DBCD. In other words, social disparities in lifestyle that lead to increased T2D risk are mediated by AL.

6. Allostatic Load in Lifestyle Interventions

There is a small body of interventional evidence related to reducing AL.[48] In a study by Carroll et al.,[49] three intervention strategies were applied for four months in older adults with insomnia to improve their sleep quality and simultaneously reduce the prevalence of abnormal values of eight AL biomarkers. The first group of participants completed cognitive behavioral therapy including behavioral strategies to improve mood and manage daytime cognitive activity. The second group participated in weekly Tai Chi Chih and practiced slow-paced movements designed to learn control over physical function and arousal. The last group attended a sleep seminar where they received information about sleep hygiene and various factors contributing to sleep problems.[50] After 16 months of follow-up, the results showed significant improvements in sleep quality as well as AL biomarkers in participants attending cognitive behavioral therapy or Tai Chi

Chih.[49] The impact of dietary intervention on AL was assessed in a study by Soltani et al.[51] including women who were overweight or obese aged 20-64 years. Two types of intervention were applied: a diet based on the Dietary Guidelines for Americans in the first group and a Typical American Diet in the second group. Although the results did not show a difference in AL change between the two interventions, there was a strong inverse association between AL and diet quality improvements defined as lower sodium intake and higher vegetable consumption. However, the positive effects of eating less sodium and more vegetables on AL was somewhat obscured by the presumed stressful effects of shifting to a diet of higher quality (i.e., Typical American Diet to Dietary Guidelines for Americans).[51] Another study assessed the impact of 6 months of an exercise intervention on AL in 144 postmenopausal metabolically unhealthy Black women[52]. The intervention consisted of supervised, facility-based aerobic exercise intervention in the first group and home-based exercise intervention in the second group. The results showed significant decreases in AL in both intervention groups, compared to controls.[52]

Overall, there are a limited number of studies directly assessing interventions on AL, in large part due to the lack of inclusion of the AL concept in lifestyle medicine research. Nevertheless, the impact of interventions on AL can be evaluated retrospectively. Various biomarkers used to calculate AL are commonly measured in intervention trials, particularly those in the cardiometabolic space. For example, Tan et al.[53] analyzed data from diabetes prevention program intervention performed in African American women[54], and the results showed a significant reduction in the AL score.

In short, exposure to a stressful environment instigates allostatic physiological adjustment of homeostatic set-points to promote successful adaptation. Thus, increased appetite, adipogenesis, obesity, and insulin resistance can be understood as a survival response, though with prolonged stress and mounting AL, cardiometabolic risk accrues and an unhealthy state evolves.[55] Lifestyle interventions are promising strategies for AL reduction.[22]

Conclusion.

Allostatic load results from chronic exposure to social and environmental stressors and is strongly associated with DBCD risk. The association critically involves lifestyle, and AL can act as a predictor and/or consequence of an unhealthy lifestyle. Based on the current evidence, several conclusions can be made.

First, there are many research gaps requiring both retrospective and prospective study of prevention with respect to DBCD. Second, there are many knowledge gaps that require education about AL and its incorporation into lifestyle medicine training. Third, there are many clinical practice gaps where SDOH as well as transcultural factors that increase AL need to be incorporated into diabetes preventive care plans. The biological complexity permeating DBCD prevention efforts mandates a fresh look at potential interventions, with new lifestyle medicine approaches at the forefront.

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Conflict of interest

JM reports receiving honoraria from Abbott Nutrition for lectures and serving on the Advisory Board of Twin Health. The rest of the authors declare that there is no conflict of interest.

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Figure 1

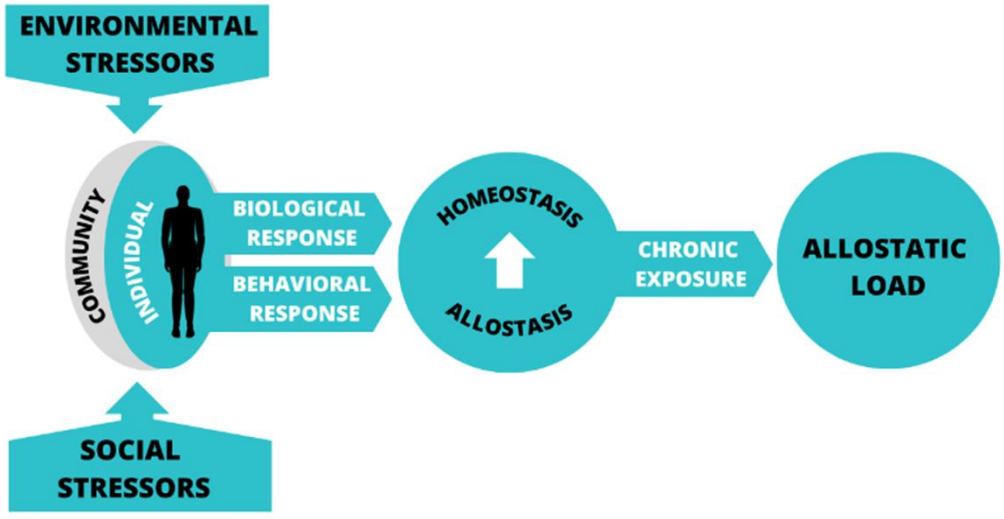

Figure 2