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Metabolic Disorders: From Principles to Practice

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Metabolic disorders (caused by genetic mutations leading to missing or dysfunctional metabolic enzymes) occur when the body is unable to process fats (lipids), proteins, sugars (carbohydrates) or nucleic acids to maintain normal physiologic homeostasis. Examples of metabolic disorders include obesity, hyperthyroidism, hypoythyroidism, diabetes, dyslipidemia, hypolipidemia, galactosemia and phenylketonuria. Metabolic syndrome is a disorder of energy utilization and storage, diagnosed by a co-occurrence of three out of five of the following medical conditions: abdominal (central) obesity, elevated blood pressure, elevated fasting plasma glucose, high serum triglycerides, and low high-density cholesterol levels. Metabolic syndrome increases the risk of developing cardiovascular disease, particularly heart failure, and diabetes[1-3]. The prevalence of metabolic syndrome increases with age and the primary pathological process was believed to be insulin resistance or hyperinsulinemia but other etiological factors are now widely linked to the development and progression of metabolic syndrome, including an altered inflammatory state, visceral adipose tissue abnormalities, and the activation of the sympathetic nervous system[1-3].

The incidence of diabetes worldwide is exacerbated by the growing obesity problem. Once thought of as primarily a childhood disease--sometimes referred to as juvenile diabetes, now mostly type 1 diabetes--the obesity crisis linked to the adoption of a high-fat, high-carbohydrate (and high-calorie diet) with increasing parallel to diseases of overt inflammation including Type 2 diabetes[4-8]. Although many metabolic abnormalities occur with obesity and type 2 diabetes, insulin resistance and hyperinsulinemia appear to be central to these conditions and may contribute to dyslipidemia and altered levels of circulating estrogens and androgens. Metabolic syndrome reflects a confluence of inflammatory conditions that occur along with the diabetes and growing evidence appears to show that metabolic syndrome makes the diabetic patient susceptible to degenerative health conditions such as cardiovascular disease, stroke and, as now believed, Alzheimer's disease and cognitive decline. Aging is a gradual and complex process in which cells, tissues, organs and the whole organism itself deteriorates in a progressive and irreversible manner that, in

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the majority of cases, implies pathological conditions that affect the individual's quality of life. The process profoundly impacts the brain and causes deterioration of neuronal and mitochondrial membranes, which leads to the loss of cellular integrity and impaired neuronal function.

The facets of cognitive decline in aging and type 2 diabetes is depicted in **Figure 1**. The incidence of dementia by age is increased in people with diabetes compared with those without diabetes[7,8]. Unlike the slight diabetes-associated cognitive decrements, the incidence of dementia is strongly dependent on age. Dementia is generally preceded by a stage in which patients have cognitive complaints and objective disturbances on cognitive testing, but in which their daily functioning is largely preserved. This stage is referred to as mild cognitive impairment (MCI)[7,8] and represents an intermediate stage between normal cognitive functioning and dementia, although not all people with MCI will develop dementia. Prospective population-based studies link type 2 diabetes to an increased risk of MCI. In people with MCI, diabetes is associated with increased conversion rate to dementia. This may be higher in people with MCI with pre-diabetes, compared with people with MCI without diabetes. Interestingly, in patients with early Alzheimer's disease, diabetes might also increase the rate of functional decline, although this effect seems to attenuate with longer duration of Alzheimer's disease. The reader is referred to the seminal review of Biessels et al[8]. Patients with severe mental disorders are at even higher risk than the general population for obesity, cardiometabolic risk factors, and related morbidity and mortality. In addition to medical consequences, obesity in the mentally ill can cause treatment nonadherence and decreased quality of life as reviewed in Correll et al[9].

The understanding of the mechanisms underlying antipsychotic cardiometabolic adverse effects will enable major inroads to the identification of high-risk patients, low-risk antipsychotics and preventive/ameliorative treatments. As observed by Correll et al[9], emerging clinical, molecular, and genetic data suggest that (1) antipsychotic-naïve samples provide the greatest power for mechanistic studies; (2) weight and metabolic effects can be discordant, pointing to overlapping and distinct mechanisms; (3) antipsychotics affect satiety and energy homeostasis signaling; (4) the specific peptides mediating these effects are unknown but likely overlap with those involved in idiopathic obesity; and (5) that firm understanding of the profile of single nucleotide polymorphisms in genes encoding known neurotransmitter receptors and metabolic proteins are promising pharmacogenomic targets for the countering of observed adverse effects[9-11]. Pharmacogenetics is the study of genetic causes of individual variations in drug response and pharmacogenomics more broadly involves the genetic determinants of drug efficacy and toxicity. That pharmacogenomics connects genotypes to patient-specific treatment intrinsically implies the existence of allelic variations in the composition of individuals genetic characteristics could be significant in tailoring disease management embracing the right drug, the right dose and the right patient concept. The allelic variations can affect the availability of functional proteins which will ultimately impact functional homeostasis and hence the outcome of drug therapy. Although there is much promise for pharmacogenomics in global healthcare, a firm understanding of the genetic basis of diseases and treatment of pathologic conditions using pharmacogenomics principles by primary care physicians, pharmacists, nurses and related healthcare professionals remain paramount[11].
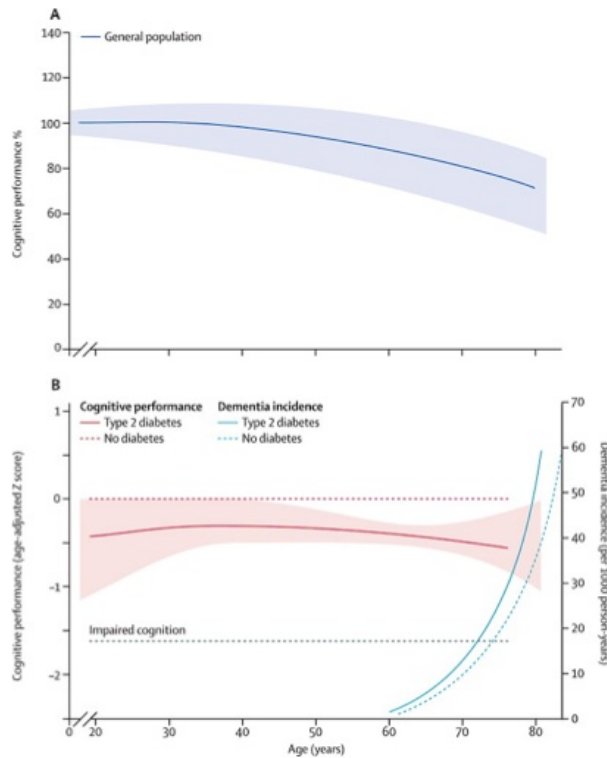
Figure 1: (A) In the general population, performance on most cognitive domains decreases slowly from midlife (about 40 years old) onwards. The shaded area represents the variation in the rate of decline between individuals. (B) The dashed red line shows mean performance of people without diabetes, normalized for age. The red line shows the slight decrements in people with type 2 diabetes across different age groups. Uncertainty of the estimates is highest in young and very old age groups, because of few studies. Mean performance in people with diabetes stays well above the threshold for impaired cognition. The blue curves on the right show the incidence of dementia by age, with incidence rates on the right y axis. *(Source: Biessels GJ, Strachan MWJ, Visseren, FLJ, Kappelle LJ and Whitmer RA (2014). Dementia and cognitive decline in type 2 diabetes and prediabetic stages: towards targeted interventions. The Lancet Diabetes & Endocrinology, 2: 246 – 255, with permission Copyright © 2014 Elsevier Ltd All rights reserved).*

This issue of 'Archives of Medical and Biomedical Research' contains papers focused on several aspects that embrace the metabolic diseases discussions. Neergheen et al[12] assessed the alterations in the antioxidant status of patients suffering from diabetes mellitus and associated cardiovascular complications. Given the background that oxidative stress and decreased antioxidant defense lead to a number of pro-atherogenic events such as LDL oxidation, endothelial dysfunction, and vascular smooth muscle proliferation and migration, a study was conducted to assess the extent of blood

biochemical parameters variation with the aim of providing meaningful data on the total plasma antioxidant activity in type 2 diabetes mellitus subjects with or without demonstrated macro-vascular complications as well as the extent of erythrocyte catalase deficiency that has been reported as a risk factor associated with diabetes was also assessed. The authors report that *in vivo* antioxidant defense was highly compromised in patients with diabetes and associated cardiovascular complications although they were on medication, thereby suggesting the potential contributory

beneficial effects of exogenous antioxidants. Davis et al[13] introduced the concept of metabolic factor: A new clinical tool in obesity diagnosis and weight management. The metabolic factor could also prove clinically useful in making decisions as to surgical interventions for obesity. The authors indicate that, given the efficiency of digesting food among people with low metabolic factors, procedures that produce malabsorption might be more appropriate. Individuals with higher metabolic factors might be able to lose weight naturally and should focus initially on behavioral aspects of weight management prior to surgery.

Kaats et al[14] report the outcome of a single group, open-label, pilot study of a weight loss formula designed to improve body composition by facilitating loss of body fat without concomitant loss of fat-free mass. The authors examined the safety and efficacy of a novel formula designed to create positive changes in mechanisms affecting body composition and point out that whilst a potential benefit of using a multi-mechanistic, instead of a single-mechanistic, approach to overcome fat accumulation, appetite control, increased energy expenditure, and favorably influencing hormonal shifts, using changes in scale weight or BMI, as opposed to changes in body composition, as an outcome measure can distort a study's conclusions. The potential impact of hyperglycemia induced oxidative damage on cellular integrity is the focus of a paper by Boyer et al[15]. Several underestimated factors at the adipocyte level could be involved in adipose tissue malfunctioning in diabetes including proteasome proteolytic complex. The intracellular protein degradation is an intricately regulated process that maintains protein homeostasis and exerts quality control by degrading damaged or misfolded proteins. In eukaryotic cells, the majority of intracellular proteins are degraded by the ubiquitin-proteasome system. Thus given that proteasomes are

modulators of oxidative stress in a variety of settings, it is important to determine the role in adipose tissue and hyperglycemia. Oxidative stress drives the activation of inflammatory processes though RAGE (advanced glycation end products receptors) ligands and receptors that can perturb insulin signaling leading to glucose intolerance and diabetes. Given the high metabolic demand for energy in the brain, perturbations in glucose metabolism can noticeably impact cognitive performance[16]. Aruoma et al discuss and enlighten on the factors contributing to cognitive impairment in Type 2 diabetes mellitus[16]. An understanding of the mechanisms of diabetes-related cognitive impairment and the resulting behaviors of patients can help healthcare professionals implement treatments to significantly improve health status and quality of life of patients with diabetes. The use of available therapeutic drugs coupled with nutraceutical adjuncts could represent a potential therapeutic strategy for the reduction of mental-health consequences and serve as a preventive measure for at-risk individuals (**Figure 1**). The prevalence of diabetes in the elderly is growing as a result of both the increase of life expectancy and incidence of diabetes in the general population. It is understandable that the consequences of diabetes can exacerbate degenerative complications and the effects of co-morbidities. Complications extending to the central nervous system may have a deteriorating effect on mental health including a decline in cognitive functioning. This could be a reason for depression, lack of compliance towards medication/treatment, and the inability of patients to meet the day-to-day management demands of the disease.

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REFERENCES

1. Lake JE, Currier JS. Metabolic disease in HIV infection. *Lancet Infect Dis*. 2013;13(11):964-75.

2. Shin JA, Lee JH, Lim SY, Ha HS, Kwon HS, Park YM, et al. Metabolic syndrome as a predictor of type 2 diabetes, and its clinical interpretations and usefulness. *J Diabetes Investig*. 2013;4(4):334-43.

3. Raven GM. Banting lecture 1988. Role of insulin resistance in human disease. *Diabetes*. 1998;37(12):1595-607.

4. Aruoma OI, Neergheen VS, Bahorun T, Jen L-S. Free radicals, antioxidants and diabetes: embryopathy, retinopathy, neuropathy, nephropathy and cardiovascular complications. *Neuroembryol Aging*. 2007;4(3):117-37.

5. Louie SM, Roberts LS, Nomura DK. Mechanisms linking obesity and cancer. *Biochim Biophys Acta*. 2013;1831(10):1499-508.

6. Ferguson RD, Gallagher EJ, Scheinman EJ, Damouni R, LeRoith D. The epidemiology and molecular mechanisms linking obesity, diabetes, and cancer. *Vitam Horm*. 2013;93:2013;51-98.

7. Ferri CP, Prince M, Brayne C, Brodaty H, Fratiglioni L, Ganguli M, et al. Global prevalence of dementia: a Delphi consensus study. *Lancet*. 2005;366(9503):2112-7.

8. Biessels GJ, Strachan MWJ, Visseren, FLJ, Kappelle LJ, Whitmer RA. Dementia and cognitive decline in type 2 diabetes and pre-diabetic stages: towards targeted interventions. *Lancet Diabetes Endocrinol*. 2014;2(2):246-55.

9. Correll CU, Lencz T, Malhotra AK. Antipsychotic drugs and obesity. *Trends Mol Med*. 2011;17(2):97-107.

10. Miron IC, Baroană BC, Popescu F, Ionică F. Pharmacological mechanisms underlying the association of antipsychotics with metabolic disorders. *Curr Health Sci J*. 2014;40(1):12-17.

11. Aruoma OI. Pharmacogenomics in biomedicine and personalized healthcare. *Arch Basic Appl Med*. 2013;1(1):1-3.

12. Neergheen-Bhujun VS, Seenauth-Beesoo V, Joonas N, Aruoma OI, Bahorun T. Alterations in the antioxidant status of Mauritian patients suffering from diabetes mellitus and associated cardiovascular complications. *Arch Med Biomed Res*. 2014;1(2):35-46.

13. Davis B, Indelicato J, Joonas N, Kuiper N. Metabolic factor: a new clinical tool in obesity diagnosis and weight management. *Arch Med Biomed Res*. 2014;1(2):47-53.

14. Kaats G, Scheckenbach R, Bagchi D, Leckie RB, Preuss HG. Single group, open-label, pilot study of weight loss formula designed to improve body composition by facilitating loss of body fat without concomitant loss of fat-free mass. *Arch Med Biomed Res*. 2014;1(2):54-65.

15. Boyer F, Rondeau P, Bourdon E. Hyperglycemia induces oxidative damage in SW872 cells. *Arch Med Biomed Res*. 2014;1(2):66-78.

16. Aruoma OI, Narrain D, Indelicato J, Bourdon E, Murad F, Bahorun T. Cognitive impairment in patients with Type 2 Diabetes Mellitus: Perspectives and challenges. *Arch Med Biomed Res*. 2014;1(2):79-89.