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Original Research Article **Mental Health**

The Metabolic Syndrome And Specific Populations At Risk: Can Precision And Individualized Medicine Change Things?

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Abstract

Objectives of the study: the metabolic syndrome (MS) consists of a group of metabolic alterations that have insulin resistance as their common denominator and identifies a pathophysiological condition at high risk of developing cardiovascular disease and type 2 diabetes. 20% and 30% of the adult population is affected by MS Design and method: in this article the authors try to make a scientific contribution regarding the problems of some patient populations often having to necessarily take drugs with an important metabolic impact while developing an iatrogenic-based MS (IMS) and propose to further investigate the aspects and the clinical pharmacological problems of the population of psychiatric patients at risk of MS. Results: Although the prevalence of MS has been observed to be often higher in the urban population of some developing countries, there are patient populations who develop MS due to the extensive use of certain drugs with obesogenic-metabolic adverse effects, in particular some generations of antidepressant and neuroleptic drugs (NL) used in mental disorders and antiretroviral drugs, such as integrase inhibitors used in HIV infection. Conclusions: Populations at risk of IMS should be at the center of the search for an individualized precision medicine with the careful choice of pharmacological therapies and appropriate lifestyle. Unfortunately, precision medicine in the psychiatric field seems to be stopping its growth due to the lack of identification of biomarkers and indicators of psychopathology.

Keywords: Metabolic syndrom, insulin resistent, diabetes, neuroleptic, precision medicine.

INTRODUCTION

MS, formerly called syndrome X, consists of a group of metabolic alterations that have insulin resistance (IR) as their common denominator and identifies a pathophysiological condition with a high risk of developing cardiovascular disease and type 2 diabetes. estimate between 20% and 30% of the adult population is affected by MS [1] Although the prevalence of MS has been observed to be often higher in the urban population of some developing countries, there are patient populations who develop an MSI due to the wide use of some drugs with obesogenic-dysmetabolic adverse effect, such as some generations of second generation antidepressant and neuroleptic drugs (NLSG) used in mental disorders and antiretroviral drugs, such as integrase inhibitors used in HIV infection.

The prevalence of MS is increased compared to the general population in psychiatric patients, reaching 35.3% of patients with schizophrenic disorder (SD) treated with NL (Mitchell et al., 2013) [2]. Patients with psychiatric disorders have a 10-year shorter life expectancy than the general population, and the prevalence of obesity is nearly double in adults with psychiatric disorders than in others. Adults with bipolar disorder (BD) are over 60% more likely to have obesity than those without this disorder. Obesity appears to be correlated with higher BD severity [3].

A retrospective epidemiological study (Buse J. B et al., 2003) reported that the prevalence of diabetes mellitus (DM) in schizophrenic patients was approximately 20%, three times higher than that observed in the general population [4].

Precision medicine

Precision medicine encompasses a vast pool of individual data: clinical, genetic, life, and other biomarker information with a personalized approach (an integral part of the physician-patient report) The process includes a series of feedback, there is no stable endpoint, and furthermore, the cycle involves continuous precise and focused efforts. The finest and most accurate stratifications are overall intermediates of the process [5].

Precision medicine aims to provide the best available care for each patient based on stratification into disease subclasses and with a common biological basis of the disease.

Another important step is given by the patient's data evaluation in order to evolve and refine the individualization process [5]. The deep phenotyping of individuals is an integral part of the process defined as the precise and complete analysis of phenotypic anomalies in which the individual components of the phenotype are observed and described [6]. The subclasses and translation of the data used in clinical practice will depend on from computational systems and algorithms designed to acquire, archive, and exchange phenotypic data to be integrated with other variations, clinical information, and omic profiles [5, 6].

Recent advances in our understanding of the genomics and pathological architecture of diabetes and its complications have provided the framework for the development of precision medicine to personalize diabetes prevention and management. Although progress has been made in genetic and pharmacogenetic research, ongoing efforts are needed to translate and incorporate genetic information into a risk prediction model [5, 7].

The future direction of precision medicine against polygenic and multifactorial metabolic disorders including MS is based on multi-omic combinations and corresponding analyzes The identification and implementation of multi-omic data based on clinical practice remain the greatest challenge. The interpretation of multi-omics studies, (metabolomics dealing with current biological processes, epigenetics, and transcriptomics dealing with how the changes in proteins and metabolites take on during illness) is fundamental for the complete analysis of metabolic diseases including diagnosis and treatment [8].

The application of precision medicine in psychiatry is in its early stages. Psychiatry is based on clinical judgment and on diagnostic (phenomenology), and pharmacological guidelines [9].

There are more and more predictive models based on clinical data or combinations of neuroimaging and biological data. These models have also begun to be applied for clinical situations such as lithium response, antidepressant resistance in major depressed disorder or as risk stratification and outcome prediction in schizophrenia [10]. The genetic variants associated with psychiatric dists with multifactorial etiology still show a necessary evolution especially because the relationship between genotype-phenotype of psychic disorders is elusive, so also the individual response to the drug treatment can be influenced by genes or by the genetic polymorphism. It is hypothesized that epigenome analysis as an interface between the genome and the environment plays a fundamental role. In the last decade, a new technology of implementation of next-generation sequencing (NGS) has been put in place, which has allowed the sequencing of the whole genome using generic targeted panels (WEG) - while previously genetic tests were performed on rare diseases with recurrent mutations of a single gene [11].

Pathophysiology of MS

MS consists of a group of metabolic alterations associated with obesity, atherogenic dyslipidemia (AD), arterial hypertension, changes in blood glucose and identifies a pathophysiological condition at high risk of developing cardiovascular disease and type 2 diabetes.

MS is diagnosed when a patient has diabetes or impaired glucose tolerance or IR and two or more of the following conditions: abdominal obesity, changes in triglycerides, decreased HDL cholesterol, changes in blood glucose above the normal threshold, high blood pressure, albuminuria and creatininuria Table 1.

Table 1: (World Health Organization Clinical Criteria for MS) [12]

Parameters	Male	Female
BMI and/or waist hip.circumference ratio	>30kg/m2 >0,9	>30kg/m2 >0,85
Fasting blood glucose	>110 mg/dl	> 110 mg/dl
triglycerides	>150 mg/dl	> 150mg/dl
HDL cholesterol	<40mg /dl	<50mg/dl
Art pressure or hipertensive treatment	>140/90mmHg	>140/90
albuminuria	>20 mg/min	> 20 mg/min
creatininuria	>30 mg/g	>30 mg/g

The presence of IR, visceral adiposity (VA), AD and endothelial dysfunction (ED) are the main characteristics of MS. These features are related to each other and share common pathophysiological mechanisms.

RE, VA and individual predisposition to these two characteristics seem to be necessary for the development of MS and for the expression of the phenotype. VA causes a decrease in insulin-mediated glucose uptake contributing to IR with the involvement of adipokines, which modulate the exchange between metabolism and vascular function and the involvement of proinflammatory factors such as tumor necrosis factor α and interleukin-6, which help maintain IR and vascular dysfunction.

AD follows from IR and VA, while ED,in addition to being correlated to IR, derives from adipokines and free fatty acids that are released from visceral adipose tissue. Both AD and ED conditions mechanically contribute to the development of atherosclerosis and cardiovascular disease [13]. The lifestyle of these patients involves exposure to risk factors and environmental factors (improper diet, sedentary lifestyle, cigarette smoking, use of substances or alcohol, low economic status).

Pharmacological molecules and adverse events in clinical practice.

The advent of NLSG since the nineties, if on the one hand they have considerably reduced the side effects produced by the first generation NL (parkinsonism, arterial hypotension, risk of cardiac toxicity, etc.), on the other hand it has been evaluated after years the metabolic impact with major risks for the development of IMS [14]. The risk of DM and weight gain and hyperlipidemia varies according to the types of NLSG involved Table 2.

Table 2: NL and risk of diabetes and impaired glucose tolerance and obesogenic effect (modified from Maudsley Prescribng Guidelines in psychiatry 13 and 2018 tab 1.30 p126) [15]

Drugs NL	Degree of Risk
Clozapine,olanzapine	high
Quetiapine,risperidone, phenothiazines	moderate
NL high power I gen.(haloperidol)	low
Aripiprazole,amisulpride, brexpiprazole,cariprazine, asenapine,lurasidone, ziprasidone	minimum

Olanzapine and clozapine are associated with the highest risks, risperidone quetiapine and paliperidone with relatively low risks. Furthermore, weight gain is related to the duration of treatment (within the first 12 weeks) and is dose-dependent [15-17]. These adverse effects have become an obstacle in the treatment of disorders which in addition to compensating for the psychopathological picture aims to improve patients' quality of life globally.

The metabolic effects of NLSG seem to be caused by the histaminergic affinity for the antagonizing action for the histamine H1 receptor (sedative effect) and the serotonin 5HT2c receptor which seem to have a role in the regulation of appetite and for action also at the level paraventricular hypothalamic AMP kinase and arcuate nucleus [18].

Some studies have correlated the increase in prolactin with weight gain, while the increase in leptin correlated with the increase in the storage of abdominal adipose tissue and a decrease in hypothalamic sensitivity [19].

Pharmacological research in the 2000s gave the first third generation NL that has aripiprazole as its parent, then followed by cariprazine, and lastly brexipiprazole. These new NLs have a pharmacological action of partial agonism on dopaminergic D2 receptors (antipsychotic effect) and multimodal receptor action, with very little or no metabolic impact [20].

However, in clinical practice, the correlation between NL dosage, weight gain and psychopathological symptoms is complex, because it seems to be more influenced by the severity of the symptoms.

This leads to the deduction that behavioral disorders in severe cases affect the lifestyle and treatment of psychopathology more with the use of other categories of psychotropic drugs present or associated with each other in polytherapy such as valproic acid and carbolithium with NL and antidepressants.

Most people with HIV infection suffer from significant weight gain and metabolic disturbances related to antiretroviral therapy. Treatment with integrase inhibitors, in particular, leads to increases in body mass index, overweight and obesity. The causes are currently unknown, and these conditions may increase the risk of cardiovascular events and complications related to dysmetabolism [21].

RESULTS AND DISCUSSION

Today with the advent of precision medicine, that is personalized and targeted, which takes into

account gender, individual, microbiota differences and tends to be applied to the stratification of patients, sometimes referred to as a new taxonomy, and this is derived using large data scale that includes clinical, lifestyle, genetic and additional biomarker information, surpassing the symptom-based approach [22].

As far as psychiatric sciences are concerned, precision medicine does not develop as for other medical disciplines, for example the psychobiological mechanisms of clinically relevant symptoms obtained from innovative integrative methodologies applied in IMAGEN should allow the identification of symptom groups based on mechanisms shared psychobiology and the development of markers that predict disease course and response to treatment in clinical groups. These improvements in psychiatric precision medicine will hopefully be achieved, in part, in the future [23].

In addition, psychiatric genomics is providing information on the nature of psychiatric conditions that over time should identify new drug targets and improve patient care, while pharmacogenymics despite having the potential to bring about more rapid changes in clinical practice and psychiatric research. it appears not to have had the necessary impact on clinical management in psychiatry. Lack of progress such as a lack of large-scale replication studies, inconsistencies in defining valid treatment outcomes between experiments, the inability to routinely incorporate adverse drug reactions and serum metabolite monitoring into study designs, and a inadequate investment in the longitudinal data collections needed to demonstrate clinical utility [24].

CONCLUSION

Populations at risk of IMS should be at the center of the search for an individualized precision medicine with the careful choice of specialized pharmacological therapies with lower metabolic impact and an appropriate lifestyle, aimed at avoiding secondary prevention. In order to achieve satisfactory goals, patients and physicians must consider both weight loss, weight maintenance and improvement of the risk factors associated with this condition, particularly cardiovascular risk. Pharmacological control of blood glucose, hyperlipidemia, blood pressure and where necessary the use of metformin, antiaging agents and antihypertensive agents.

In the treatment of mental disorders, despite the choice of NL with low metabolic impact, it is often necessary to resort to polytherapy with different classes of molecules that contribute to increasing the weight weight. Therapeutic interventions must increasingly be interdisciplinary and within a treatment path with clear objectives.

Although precision medicine has been considered by the European Commission since 2013 [25] and is progressing with interest also in Eastern countries in various fields of medical sciences, in the psychiatric field it is experiencing a slowdown in growth mainly due to the lack of clear biomarkers and biological indices of psychiatric pathologies that affect the stratification of large-scale data, the possibility of prevention and early intervention strategies.

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