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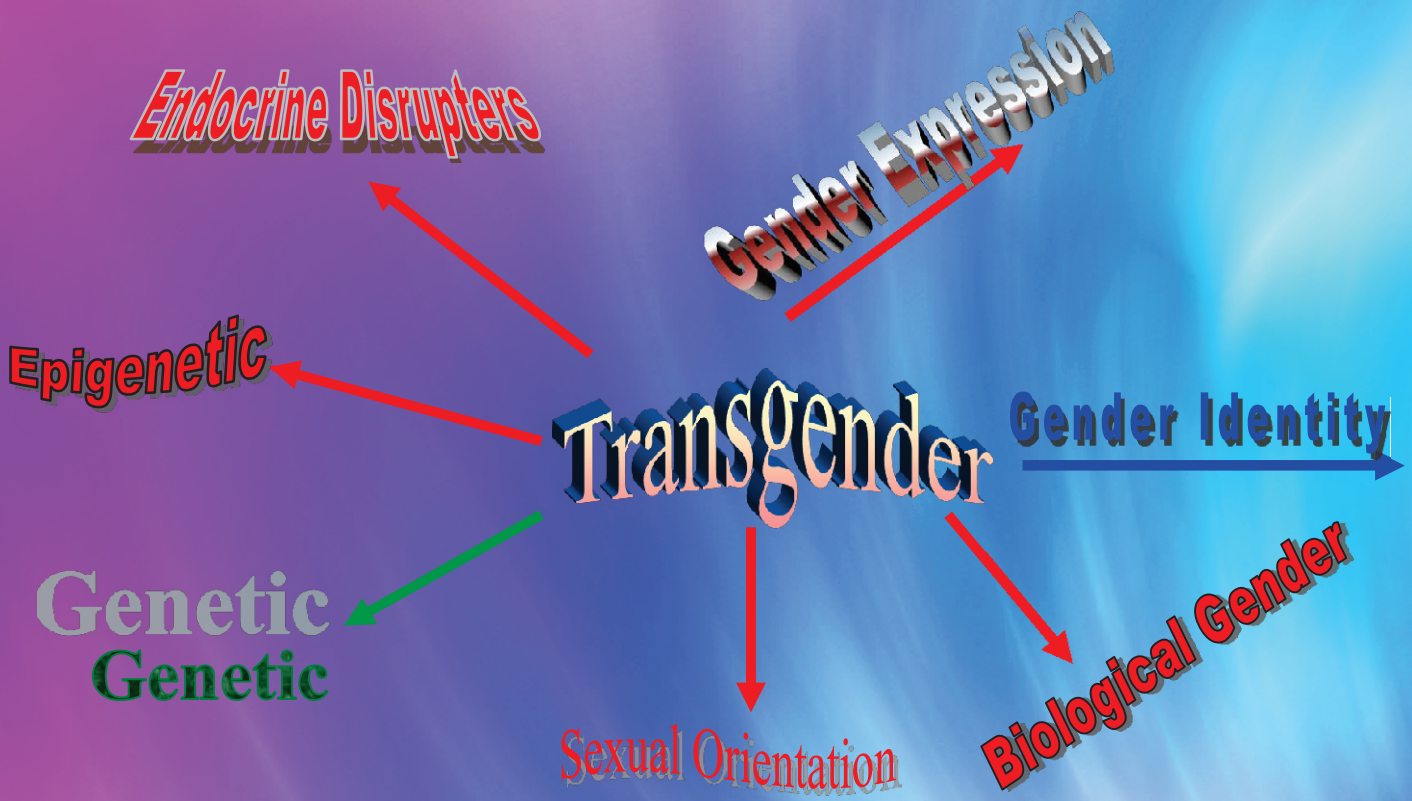

EDITORIAL

"TO BE A TRANSGENDER IS THE MAJOR LIFE TRANSITION"

What does it mean to be a transgender?

Transgender is not a mental disorder and the first country to declassify it was Denmark.

In 2013 the ***gender identity*** disorder was changed in the **Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DM5)** and a new condition called ***gender dysphoria*** was added to diagnose and treat patients who felt distress with the identity of their bodies (1). From that time on, the new sex identity was not considered neither pathological nor disease. As a consequence, psychiatric intervention can be done only when the patient fell distress, depression, behavior disturbs or suicidal ideation. The human being have the right to pursue life on their own terms submitting theirselves to surgeries for body changes. The transgender is a subject like me, like you; **they** are fathers, mothers, brothers, sisters, daughters and sons. They are 8 or 60 years old. They have existed in every culture and recorded history, but only now in this century they could fit their own identity.

Nowadays there is perspective on transgender medicine including surgical and hormones treatment. Studies showed biological bases for gender identity such as steroids hormones, the genetics of their receptors and neuroanatomical alterations such as grey and white matter in brain. In the journal Endocrine Practice, Joshua D. Safer explains that the gender identity is a biological phenomenon and it is not a psychiatric disease (2). Biological evidences may change the resistance of physicians in hormonal and surgical treatment providing good care for these individuals.

What a transgender needs to live well? (3)

Legal Protection: Creation of laws against discrimination; access to public bathrooms that correspond with their gender identity;

Employment: Without discrimination;

Stigma: The society must understand transgenders and never submit them to ridicule;

Anti-transgender violence: Laws and justice to protect them from hate, intolerance, violence and homicides;

Access to health care: The transgender community needs to have access to health service equal to other people;

Identity documents: It is important to have their identity documents as quick as possible without fees to match their affirmed gender.

Unfortunately, we all know these changes will not come in a fast way. For an adequate social integration of transgenders it is necessary to educate and elucidate society through human rights campaign in schools and community (2,3).

Editors of Revista de Endocrinologia & Diabetes - Clinica e Experimental

1. Scientificamerican.com. Acessed in July 2017

2. Safer J D, Endocrine Practice 2015

3. Understanding the transgender community: www.hrc.org - Accessed in July 2017

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COMPUTATIONAL SIMULATION OF THE MOLECULAR STRUCTURE OF microRNA OVER-EXPRESSED IN TYPE 2 DIABETES

SIMULAÇÃO COMPUTACIONAL DA ESTRUTURA MOLECULAR DE MICRO RNA SUPEREXPRESSOS EM DIABETES TIPO 2

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Keywords: microRNA, Nucleotide analysis, Molecular structure, Type 2 diabetes
Descritores: microRNA, Análise de nucleotídeos, Estrutura molecular, Diabetes tipo 2.

Resumo

Introdução: Estudos de biologia molecular demonstram que os microRNAs (miRNAs) parecem desempenhar um papel fundamental no desencadeamento e na progressão da diabetes tipo 2 (DM2), além de ser sugerido como um novo biomarcador para a predição de DM2. Os miRNAs são pequenos RNAs não codificados com 19-25 nucleotídeos que implicam no controle pós-transcrição da expressão gênica em organismos multicelulares, desestabilizando processos como a tradução, resultando em degradação ou silenciamento de miRNAs alvos. **Objetivo:** Desenvolver uma simulação computacional da estrutura molecular de miRNA já definidos como biomarcadores para a predição de DM2. **Métodos:** Foi realizada uma pesquisa da sequência de nucleotídeos de 4 miRNAs já definidos como biomarcadores para a predição de DM2, realizando projeção silico da estrutura molecular dos seguintes miRNAs: miRNA-455-5p, miRNA-454-3p, miRNA-144- 3p e miRNA-96--5p. Os nucleotídeos foram selecionados usando o GenBank, que é o banco de dados de sequência genética do Instituto Nacional de Saúde Americano. As sequências obtidas foram alinhadas com os algoritmos Clustal W de alinhamento múltiplo. Para a modelagem molecular, as estruturas foram geradas com o RNAstruture, um servidor de modelagem da estrutura de miRNAs totalmente automatizado, acessível através do servidor da Web para a previsão de estrutura secundária do RNA. **Resultados:** Demonstramos uma busca pela sequência de nucleotídeos e a projeção da estrutura molecular dos seguintes miRNA: miRNA-455-5p, miRNA-454-3p, miRNA-144--3p e miRNA-96-5p.**Conclusão:** Neste estudo, demostramos a projeção computadorizada de estruturas secundárias de 4 miRNA definidos como biomarcador para a predição de DM2 através de biologia computacional. **Endocrinol diabetes clin exp 2017 1988 -1992.**

Abstract

Introduction: Molecular biology studies demonstrate that microRNAs (miRNAs) seem to play a fundamental role in triggering and progression of type 2 diabetes (DM2), as well as, have been suggested as a novel biomarker for DM2 prediction. The miRNAs are small noncoding RNAs with 19-25 nucleotides that implicate in post transcriptional control of gene expression in multicellular organisms by disturbing the stability in processes such as translation, resulting in target miRNAs degradation or silencing. **Objective:** To develop *in silico* projection of molecular structure of miRNA already defined as biomarker for DM2 prediction. **Methods:** A search was performed on the nucleotide sequence of 4 miRNAs already defined as biomarker for DM2 prediction, performing *in silico* projection of the molecular structure of the following miRNAs: miRNA-455-5p, miRNA-454--3p, miRNA-144-3p and miRNA-96-5p. The nucleotides were selected using GenBank that is the American National Institutes of Health genetic sequence database. The sequences obtained were aligned with the Clustal W multiple alignment algorithms. For the molecular modeling, the structures were generated with the RNAstructure, a fully automated miRNAs structure modelling server, accessible via the Web Servers for RNA Secondary Structure Prediction. **Results:** We demonstrated a search for nucleotide sequence and the projection of the molecular structure of the following miRNA: miRNA-455-5p, miRNA-454-3p, miRNA-144-3p, and miRNA-96-5p. **Conclusion:** In this study we show *in silico* secondary structures projection of selected of 4 miRNA defined as biomarker for DM2 prediction through computational biology. **Endocrinol diabetes clin exp 2017 1988 -1992.**

INTRODUCTION

Type 2 diabetes mellitus (DM2) is characterized by hyperglycemia associated with peripheral insulin resistance with action reduction of insulin activity. Thus, it is necessary to develop of biomarkers for early diagnosis, identifying subjects at risk for developing DM2. Molecular biology studies demonstrate that microRNAs (miRNAs) seem to play a fundamental role in triggering and progression of DM2, as well as, have been suggested as a novel biomarker for DM2 prediction (1).

The miRNAs are small noncoding RNAs with 19-25 nucleotides that implicate in post transcriptional control of gene expression in multicellular organisms by disturbing the stability in processes such as translation, resulting in target miRNAs degradation or silencing (2).

Recently, knowledge of the structure and role of miRNA has significantly increased. The bioinformatics programs currently available to construct molecular modeling and analyses nucleotide sequences provide tools for assembly of miRNA and understanding of their molecular mechanisms. The aim of this study was to develop *in silico* projection of molecular structure of miRNA, and a tutorial on molecular modeling of 4 miRNAs already defined as biomarker for DM2 prediction.

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METHODS

We conducted a search on the nucleotide sequence of 4 miRNAs already defined as biomarker for DM2 prediction, performing *in silico* projection of the molecular structure of the following miRNAs: miRNA-455-5p, miRNA-454-3p, miRNA-144--3p and miRNA-96-5p. The nucleotide sequences were selected using GenBank that is the NIH genetic sequence database. GenBank is part of the International Nucleotide Sequence Database Collaboration, which comprises the DNA DataBank of Japan, the European Nucleotide Archive, and GenBank at NCBI. The sequences obtained were aligned with the Clustal W multiple alignment algorithms. For the molecular modeling, the structures were generated with the RNAstructure that is a fully automated miRNA structural modelling server, accessible via Web Servers for RNA Secondary Structure Prediction (http://rna.urmc.rochester.edu/RNAstructureWeb/).

Nucleotide database search and sequence analysis

GenBank is a nucleotide sequence analysis tool available in the public domain (https://www.ncbi.nlm.nih.gov/genbank/submit/) and a wide variety of nucleotide algorithms is used to search many different sequence databases.The Nucleotide, Genome Survey Sequence (GSS), and Expressed Sequence Tag (EST) database all contains nucleic acid sequences. The data in GSS and EST are from two large bulk sequence divisions of GenBank.

Building molecular models

The structure and function of amino acid and proteins are determined by their nucleotide sequences and the structure prediction still remains a significant challenge, with a great demand for high resolution structure prediction methods.

Homology modeling is currently the most accurate computational method to generate reliable structural models and is routinely used in many biological applications.

Modeling with RNAstructure

The Predict to Secondary Structure server calculate a partition function, predict the maximum free energy structure, find structures with maximum expected accuracy, and pseudoknot prediction. This server creates a highly probable, probability annotated group of secondary structures, starting with the lowest free energy structure and including others with varying probabilities of correctness. Other structures are included because the minimum free energy structure may not be the correct one. If shape constraints are specified, the shape constraints are applied to the probability annotated structures. In addition, a second group of shape constrained, shape annotated structures will be generated. This shape structure group is distinct from the probability annotated structure group, and is not likely annotated itself.

RESULTS

We demonstrated a search for nucleotide sequence and the projection of the molecular structure of the following miRNA: miRNA-455-5p, miRNA-454-3p, miRNA-144-3p, and miRNA-96-5p.

Nucleotide sequence of miRNA-455-5p

The main data source used for reconstructing the miR-455-5p was the nucleotide sequence file in FASTA format. The full-length nucleotide of miR-455-5p was obtained from the GenBank database under the identifier NCBI: NR_030255.1. The miR-455-5p was predicted to encode a 96 bp linear. All coding sequences were selected and exported as nucleotides in FASTA format, using the annotation of the NCBI - Graphics. Homo sapiens microRNA 455 (MIR455), microRNA analysis is shown in (**Figure 1)**.

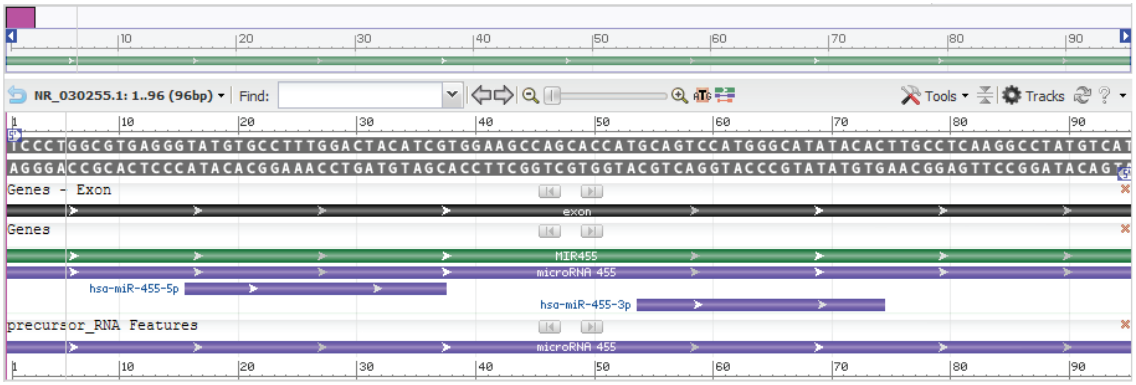

Figure 1. Homo sapiens microRNA 455 (MIR455) - *model-template aligment.*

Molecular model of miRNA-455-5p

Nucleotide sequences of Homo sapiens miRNA 455 (MIR455) were obtain using FASTA format; modeling was conducted using the RNAstructure programs, which were adjusted and optimized for alignment between miRNA-455--5p nucleotide and structural templates. On the basis of a sequence alignment between the miRNA-455-5p nucleotide and the template structure, a structural model for the target nucleotide was generated. Model quality assessment tools were used to estimate the reliability of the resulting model. Thus, using the RNAstructure programs automated comparative nucleotide modeling server, we constructed a homology model of the Homo sapiens microRNA 455 (MIR455) (**Figure 2**).

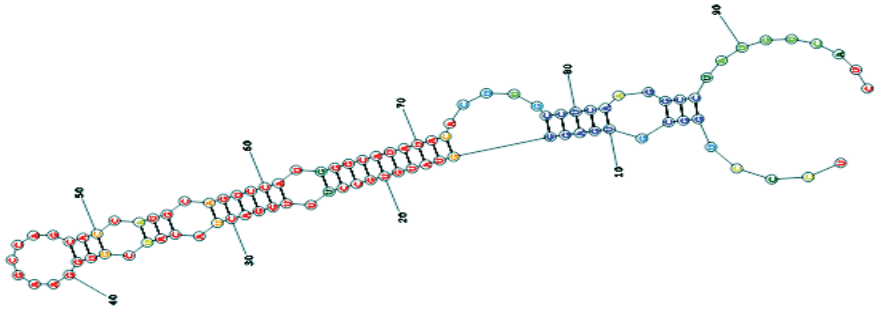

Figure 2. Homology model of the hsa-miRNA-455-5p

Nucleotide sequence of miRNA-454-3p

The reconstruction of the miR-454-3p was made from a nucleotide sequence file in FASTA format. The full-length nucleotide of miR-454-3p was obtained from the GenBank database under the identifier NCBI Reference Sequence: NR_030411.1. The miR-454-3p was predicted to encode a 115 bp linear. All coding sequences were selected and exported as nucleotides in FASTA format, using the annotation of the NCBI - Graphics. Homo sapiens microRNA 454 (MIR454), microRNA analysis is shown in (**Figure 3)**.

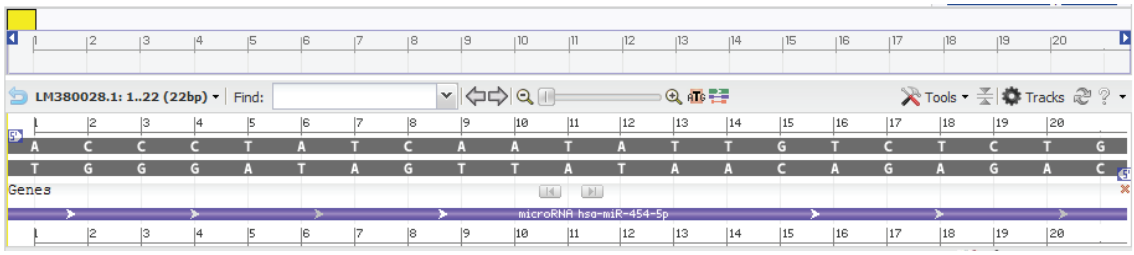

Figure 3. Homo sapiens microRNA 454 (MIR454) - *model-template aligment.*

Molecular model of miRNA-454-3p

Template search with FASTA format was performed against the RNAstructure template library, which were adjusted and optimized for alignment between Homo sapiens miRNA 454 (MIR454) nucleotide and structural templates. On the basis of a sequence alignment between the miRNA 454 nucleotide and the template structure, a structural model for the target nucleotide was generated. Model quality assessment tools were used to estimate the reliability of the resulting model. According to the described criteria, a model for the Homo sapiens miRNA 454 (MIR454) was generated (**Figure 4**).

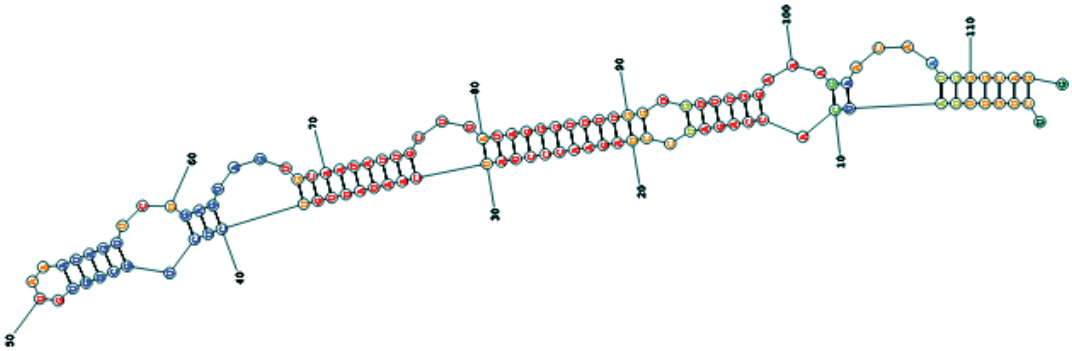

Figure 4. Homology model of the Homo sapiens hsa-miRNA-454-3p

Nucleotide sequence of miRNA-144-3p

The main data source used for reconstructing the miRNA-144--3p was the nucleotide sequence file in FASTA format. The full-length nucleotide of miR-144-3p was obtained from the GenBank database under the identifier Homo sapiens miRNA hsa-miRNA-144-3p GenBank: NR_029685.1. The miRNA-144-3p was predicted to encode a 86 bp linear transcribed-RNA. All coding sequences were selected and exported as nucleotides in FASTA format, using the annotation of the NCBI - Graphics. Homo sapiens microRNA 144 (MIR144), microRNA analysis is shown in (**Figure 5).**

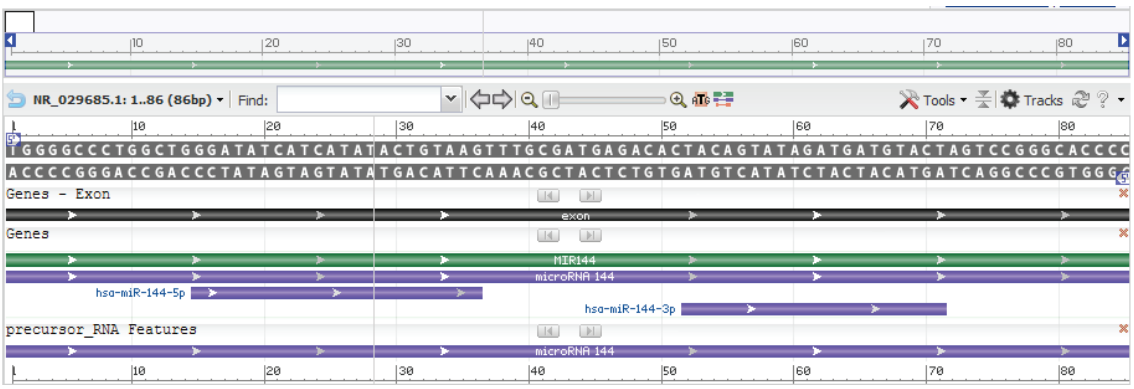

Figure 5. Homo sapiens microRNA 144 (MIR144) - *model-template aligment.*

Molecular model of miRNA-144-3p

Nucleotide sequences of miRNA-144-3p were obtain using FASTA format; modeling was conducted using the RNAstructure programs, which were adjusted and optimized for alignment between Homo sapiens miRNA hsa--miRNA-144-3p nucleotide and structural templates. On the basis of a sequence alignment between the Homo sapiens miRNA miRNA-144-3p nucleotide and the template structure, a structural model for the target nucleotide was generated. Model quality assessment tools were used to estimate the reliability of the resulting model. Thus, using the RNAstructure programs automated comparative nucleotide modeling server, we constructed a homology model of the Homo sapiens miRNA-144-3p (**Figure 6**).

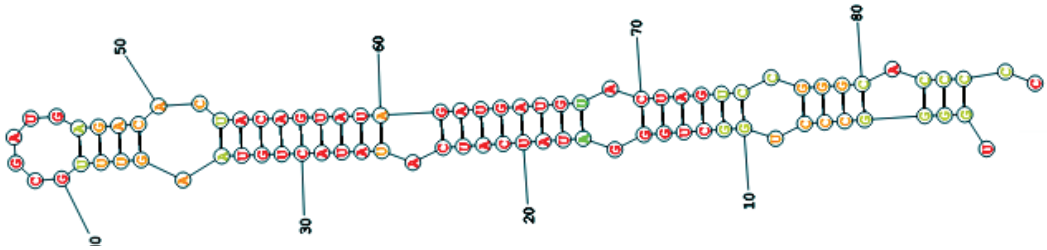

Figure 6. Homology model of the Homo sapiens miRNA-144-3p

Nucleotide sequence of miRNA-96-5p

The reconstruction of the miRNA-141 was made from a nucleotide sequence file in FASTA format. The full-length nucleotide of miRNA-96-5p was obtained from the GenBank database under the identifier NCBI Reference Sequence: NR_029512.1. The Homo sapiens microRNA 96 (MIR96), microRNA was predicted to encode a 78 bp linear non-coding RNA, miRNA. All coding sequences were selected and exported as nucleotides in FASTA format, using the annotation of the NCBI - Graphics. Homo sapiens microRNA 96 (MIR96), microRNA analysis is shown in (**Figure 7**).

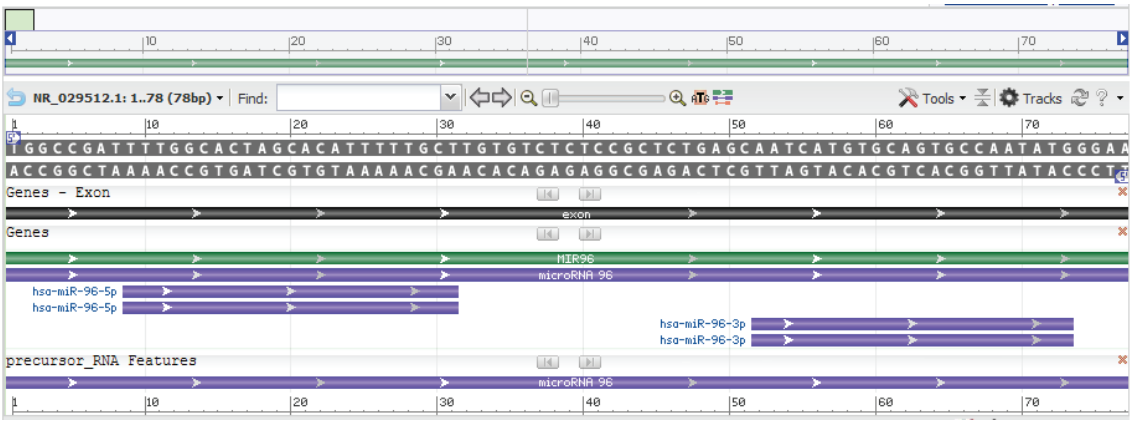

Figure 7. Homo sapiens microRNA 96 (MIR96) - *model-template aligment*

Molecular model of miRNA 96-5p

Template search with FASTA format was performed against the RNAstructure template library, which were adjusted and optimized for alignment between Homo sapiens miRNA 96 (MIR96), nucleotide and structural templates. On the basis of a sequence alignment between the miRNA-96-5p nucleotide and the template structure, a structural model for the target nucleotide was generated. Model quality assessment tools were used to estimate the reliability of the resulting model. According to the described criteria, a model for the Homo sapiens miRNA-96 (MIR96), miRNA was generated (**Figure 8**).

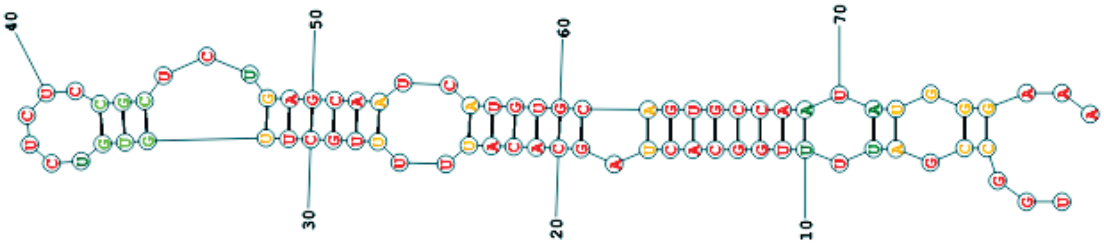

Figure 8. Homology model of the Homo sapiens miRNA-96-5p

DISCUSSION

The miRNAs are small non-protein-coding RNA that performs regulatory roles in several physiological and pathophysiological functions. In the last years, the knowledge of the structure and role of miRNA has significantly increased. In this study, we developed a tutorial on molecular modeling of 4 miRNAs already defined as biomarker for DM2 prediction. It has been demonstrated that miRNAs plays important roles in DM2, being important for its diagnosis and treatment (3).

Studies demonstrated that serum expression levels of miRNA-455-5p, miRNA-454-3p, miRNA-144-3p and miRNA-96-5p were higher in patients with DM2, when compared with those of healthy individuals (4).

The miRNA-455-5p is localized on chromosome 9q32, and was predicted computationally and the precise sequence termini of the mature forms were derived by cloning from human and rat samples (5). The miRNA-455-5p may regulate numerous miRNAs and target genes, and is involved in the MHC protein complex assembly pathway and peptide antigen assembly with MHC class I protein complex pathway. In addition, it has been demonstrated also that miRNA-455-5p is involved in the acute myocardial infarction, inhibition of tumor cell proliferation and induction of apoptosis in human colon cancer cells, is linked to hypoxia signaling and is deregulated in preeclampsia, and serve as potential biomarkers for DM2 (4,6-8).

Technological advances in post-genomic era have contributed to an expanding filling the databases and microarrays and other technologies have created a wealth of data for biologists, and the challenge facing scientists is to analyze and even to access these data to extract useful information. Several bioin-

formatics methods for miRNAs prediction have been developed, providing valuable understanding in the mechanisms of miRNAs transcriptional regulation. We researched the miRNA-455-5p sequences in the NCBI database using GenBank database under the identifier NCBI reference sequence, identifying all the nucleotide encoded in miRNA-455-5p and predicted their structure using domain analysis tools.

Recently, bioinformatics tools for the prediction of miRNAs have gained popularity because experimental studies for define miRNAs are unusual in their application. Nowadays, *in silico* evaluation of miRNA is based mostly on primary and secondary structure analysis. Reviewing the literature, we observed that none study with two-dimensional (2-D) structural model of the miRNA-455-5p was built. In our analysis, we carried out extensive the Nucleotide database that is a collection of sequences from several sources, including GenBank, RefSeq, TPA and PDB, and a 2-D model of miRNA-455-5p was built with the RNAstructure programs online.

The miRNA-454-3p is localized on chromosome 17q22 (9). Studies have shown that miRNA-454-3p promotes the progression of human non-small cell lung cancer, regulates stromal cell derived factor-1 in the control of the growth of pancreatic ductal adenocarcinoma, and their serum expression levels were higher in patients with DM2, compared with those of healthy subject (4,10,11). In addition, miRNA-454-3p can enhance cellular radiosensitivity in renal carcinoma cells by inhibiting the expression of B cell translocation gene anti-proliferation factor (12). In our study, the nucleotide analysis of miRNA-454-3p was performed in FASTA format, and the 2-D modeling used the RNAstructure program, which was adjusted and optimized for alignment between miRNA-454-3p and structural templates. Thus, in order to build a 2-D structural model of miRNA-454-3p we used the Nucleotide database sequence and a structural homology analysis strategy.

The miRNA-144-3p is localized on chromosome 17 q11.2, have functions in a cluster with miR-451, and one of your targets is insulin receptor substrate 1. In addition, this locus regulates the expression of a number of genes whose products are involved in erythropoiesis (13,14). The miRNA-144-3p has shown to be a potential novel biomarker for DM2 prediction, since express high up-regulated in DM2 and it also displays a linear relationship with increasing glycemic status (13). Moreover, microRNA-144-3p has been reported to be involved in both tumorigenesis and suppression of many types of cancers depending on the organ and the tissues, as a target potential therapeutic to treatment ischemic heart disease, bipolar affective disorder and schizophrenia (15,16). Searching in medical literature database, we observe that none scientific study demonstrating the 2-D structure model of the microRNA-144-3p was built. In this study, the nucleotide sequence of microRNA-144--3p was retrieved from NCBI sequence database, and this sequence was converted to FASTA format. The 2-D structure of microRNA-144-3p was built using RNAstructure program. Thus, in absence of 2-D structures for most of the sequenced nucleotide, homology modeling experimentally forms the basis for the resolution of structure.

The miRNA-96-5p is localized on chromosome 7q32.2, demonstrates oncogenic activities in several cancers, as well as control selective high-density lipoprotein cholesterol and cholesteryl ester uptake, and regulates endogenous lipid synthesis. In addition, the up-regulation of miR-96-5p results in impaired insulin secretion (17,18). In the analysis of the literature, we observed that none study with secundary structure model of the miRNA-96-5p was produced. We created a 2-D model of miRNA-96-5p using the RNAstructure program.

CONCLUSION

The structure and function of miRNAs are determined by their nucleotides sequences and high resolution structure prediction methods make possible to identify the location of binding sites on nucleotides of fundamental importance for applications clinical and pharmacological aspects.

In this study we show *in silico* secondary structures projection of selected of 4 miRNA defined as biomarker for DM2 prediction through computational biology.

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SPECIAL ARTICLE
GUÍAS DE DIAGNÓSTICO Y TRATAMIENTO DE DIABETES GESTACIONAL. ALAD 2016

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Palabras clave: Diabetes pregestacional, Diabetes gestacional, Embarazo, Control, Prueba de sobrecarga a la glucosa, Monitoreo glucémico
Key words: Control, Gestational diabetes, Glucose.,Glycemic monitoring, Overload test. Pre-gestational Diabetes, Pregnancy

Abstract

En los últimos años el aumento en la prevalencia de obesidad y diabetes mellitus tipo 2 (DM2), la aparición a edades más tempranas de DM2, así como el desplazamiento del embarazo a edades mayores, han conllevado un aumento de casos de diabetes *mellitas* (DM) en el embarazo. En algunos pacientes la diabetes no se diagnostica y, obviamente no se trata. Este hecho puede complicar un embarazo, especialmente en el periodo embriogénico. La aplicación de nuevos criterios de diagnóstico para la diabetes gestacional (DG), la controversia en el uso y la seguridad de los antidiabéticos orales durante el embarazo, así como el uso de determinados análogos de insulina, hacen indispensable que Latinoamérica, a través del Grupo de Trabajo de Diabetes y Embarazo de la Asociación Latinoamericana de Diabetes (ALAD), actualice sus recomendaciones. El desarrollo de estas recomendaciones se realizó en varias reuniones y trabajo conjunto del grupo. Se tuvo en cuenta el grado de nivel de evidencia, la experiencia de los referentes y la adaptación cultural según las regiones donde se implementarán las recomendaciones descritas. **Endocrinol diabetes clin exp 2017 1993 -2001.**

Resumo

In recent years the increase in the prevalence of obesity and diabetes mellitus type 2, the appearance at younger ages of diabetes mellitus type 2, and the deferral of pregnancy to older ages, has led to an increase in cases of diabetes mellitus in pregnancy. This can complicate pregnancy, especially in the embryonic period. The application of new diagnostic criteria for gestational diabetes, the controversy on the use and safety of oral antidiabetic drugs during pregnancy with diabetes, and the use of certain insulin analogs make it essential that Latin America,through ALAD's Diabetes and Pregnancy Working Group, update its recommendations. The development of the recommendations made during several meetings and joint work group, the degree of level of evidence, the experience of the referents, and cultural adaptation was taken into account according to the regions where the recommendations will be implemented. **Endocrinol diabetes clin exp 2017 1993 -2001.**

INTRODUCCIÓN

El aumento del sobrepeso y de la obesidad se acompaña, en reiterados casos, de diabetes o disglucemia no diagnosticadas y, como consecuencia, se observan casos de mujeres que se embarazan sin conocer su situación clínica o sin saber que padecen diabetes. El escenario descrito ha llevado a un incremento en la prevalencia de diabetes en el embarazo. Por otro lado, diversos estudios demuestran que el riesgo de complicaciones se correlaciona deforma directa con la elevación de la glucemia durante la gestación (1). La propuesta de nuevos criterios para diagnosticar la DG (2), y la controversia en el uso y la seguridad farmacológica de los antidiabéticos orales durante el embarazo, así como también de determinados análogos de insulina, hacen indispensable que Latinoamérica, através del Grupo de Trabajo de Diabetes y Embarazo de la ALAD, actualice sus recomendaciones.

METODOLOGÍA

Las recomendaciones se realizaron con un grupo de especialistas integrantes de la ALAD, quienes se basaron en estudios y publicaciones existentes. Se tuvo en cuenta el grado de nivel de evidencia, la experiencia de los referentes y la adaptación cultural según las regiones donde se implementarán las recomendaciones descritas. El desarrollo de las recomendaciones se realizó a partir de reuniones del Grupo de Trabajo de Diabetes y Embarazo de la ALAD; se formularon las preguntas y se delimitaron los objetivos en cuanto al alcance y jerarquización de las mencionadas preguntas. Se trabajó en forma conjunta y en subgrupos, previa búsqueda bibliográfica y desarrollo de las respuestas en forma individual. Se discutieron los contenidos. Se analizó que éstos cumplieran con criterios de pertinencia y se analizó el nivel de evidencia de la recomendación, que se adaptaron culturalmente. Esto último se describe en las tablas 1 y 2 (3).

CONTENIDOS

Definiciones y conceptos

Respecto al diagnóstico de diabetes por el valor de hemoglobina A1c (HbA1c), este grupo considera que la HbA1c no es una herramienta válida para aplicar como diagnóstico de DM (B III).

Tabla 1. Niveles de evidencia

Nivel de evidencia	
Ia	La evidencia científica procede de metaanálisis de ensayos clínicos aleatorizados
Ib	La evidencia científica procede al menos de un ensayo clínico aleatorizado
IIa	La evidencia científica procede al menos de un estudio prospectivo controlado bien diseñado sin aleatorizar
IIb	La evidencia científica procede al menos de un estudio casi experimental bien diseñado
III	La evidencia científica procede de estudios observacionales bien diseñados, como estudios comparativos, estudios de correlación o estudios de casos y controles
IV	La evidencia científica procede de documentos u opiniones de comités de expertos y/o experiencias clínicas de autoridades de prestigio

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Tabla 2. Grados de recomendaciones utilizados para la conformación de las recomendaciones

Grados de recomendación	
A (niveles de evidencia científica Ia, Ib)	Requiere al menos un ensayo clínico aleatorizado como parte de un conjunto de evidencia científica globalmente de buena calidad y consistencia con relación a la recomendación específica
B (niveles de evidencia científica IIa, IIb, III)	Requiere disponer de estudios clínicos metodológicamente correctos que no sean ensayos clínicos aleatorizados sobre el tema de la recomendación. Incluye estudios que no cumplan los criterios ni de A ni de C
C (nivel de evidencia científica IV)	Requiere disponer de documentos u opiniones de comités de expertos y/o experiencias clínicas de autoridades reconocidas. Indica la ausencia de estudios clínicos directamente aplicables y de alta calidad

Fuente: Guías de práctica clínica en el Sistema Nacional de Salud[3].

Rohlfing, et al., en el estudio NHANES III, demostraron que a los tres y cuatro desvíos estándar (HbA1c de 6.5 y 7.0%, respectivamente) por encima de la media, la especificidad se acercó al 100%, pero la sensibilidad se redujo a 42.8 y 28.3%, respectivamente, para la detección de diabetes no diagnosticada (4). Cavagnolli, et al. sugieren que el punto de corte 6.5% no sería suficiente para diagnosticar diabetes. Este concepto se refuerza en el consenso de laboratorio en diabetes de la Sociedad Argentina de Diabetes (5), documento que trata sobre convergencias, divergencias, variabilidad, puntos de corte e indicación de la HbA1c (6).

Diabetes Pregestacional

Corresponde a una mujer con diabetes *mellitus* tipo 1 (DM1), DM2 u otro tipo de diabetes que se embaraza o a una embarazada que cumple con los criterios de diagnóstico de diabetes según la Organización Mundial de la Salud (OMS)7 durante el primer trimestre. Los criterios para el diagnóstico de diabetes propuestos por la OMS son:

– Síntomas clásicos de diabetes (polidipsia, poliuria, polifagia y baja de peso) y una glucemia al azar ≥ 200 mg/dl, sin relación con el tiempo transcurrido desde la última comida.

– Glucosa en plasma venoso en ayunas ≥ a 126 mg/dl. Debe confirmarse con un segundo examen en un

periodo no superior a siete días, sin modificar los hábitos alimentarios. El ayuno se define como un periodo sin ingesta calórica de por lo menos 8 h.

– Glucosa plasmática ≥ a 200 mg/dl 2 h después de una carga de estímulo de glucosa con 75 g (5,7).

Respecto al diagnóstico de diabetes pregestacional (DPG) durante el embarazo, en el estudio HAPO (8) se compararon valores de glucosa materna y HbA1c con resultados adversos. Sobre la base de estas asociaciones, los hallazgos sugieren que la medición de HbA1c no es una alternativa útil que reemplace a la prueba de tolerancia oral a la glucosa (OGTT) en mujeres embarazadas. Si bien Rowan encontró pacientes con diagnóstico de DG por HbA1c y no con OGTT (9), este hecho podría no tener relación con la hiperglucemia, sino con el aumento de la HbA1c que se presenta en pacientes con anemia por deficiencia de hierro, como ocurre en una gran mayoría de las mujeres embarazadas. Otro estudio pone de manifiesto que el valor de la HbA1c en el momento del diagnóstico de DG no pudo ser linealmente asociado con macrosomía (10,11). Ante estas evidencias bibliográficas, este grupo de trabajo considera conveniente no recomendar la HbA1c para el diagnóstico de DM durante el embarazo (B IIb, III).

Diabetes Gestacional

Corresponde a una categoría clínica definida en la clasificación de la diabetes (Fig. 1). Es la disminución de la tolerancia a la glucosa que se manifiesta durante el embarazo y se diagnostica con: – Glucosa plasmática en ayunas entre 100 y 125 mg/dl valor repetido en dos determinaciones (en el curso de la misma semana); y/o – Glucosa plasmática a las 2 h postestímulo con 75 g de glucosa anhidra ≥ a 140 mg/dl (12). Este grupo de trabajo ha decidido, por el momento, no innovar en los criterios de diagnóstico de la DG.

Establecidos por las recomendaciones de ALAD 2007, los cuales son valores avalados por las guías *The National Institute for Health and Care Excellence* (NICE) 2015 (13).

Los fundamentos del grupo para no adherir a la propuesta de DG de la Asociación Internacional de Grupos de estudio de Diabetes y Embarazo (*International Association of Diabetes and Pregnancy Study Groups* [IADPSG]) 2010 adoptados por la Asociación Americana de Diabetes (*American Diabetes Association* [ADA]) 2011 son (14):

– El punto de corte establecido a partir del estudio HAPO para hacer el diagnóstico es arbitrario (seeligió una *odds* ratio de 1.75 por votación no unánime de los miembros). Bajo este criterio, en el estudio HAPO se elevó el porcentaje de diagnóstico de la DG promedio a 17.8% de la población de embarazadas. Entre los centros de reclutamiento se observaron valores superiores al 20% (Bangkok, 23%; Mánchester, 24.3%; Cleveland, 25%; Singapore, 25.1%, y Bellflower, 35.5%); valores promedios coincidentes con un estudio realizado en Argentina (15). No existe evidencia sobre el efecto beneficioso del tratamiento sobre la base del nuevo criterio de la IADPSG, es decir, que hasta el momento no se ha demostrado mejora de indicadores en costo- efectividad (16).

El criterio utilizado por la IADPSG es cuestionado por varias sociedades científicas al referir que su aplicación aumenta significativamente la prevalencia de DG, especialmente en poblaciones de embarazadas obesas y mayores de 30 años, convirtiéndose en un problema de difícil control para la salud pública.

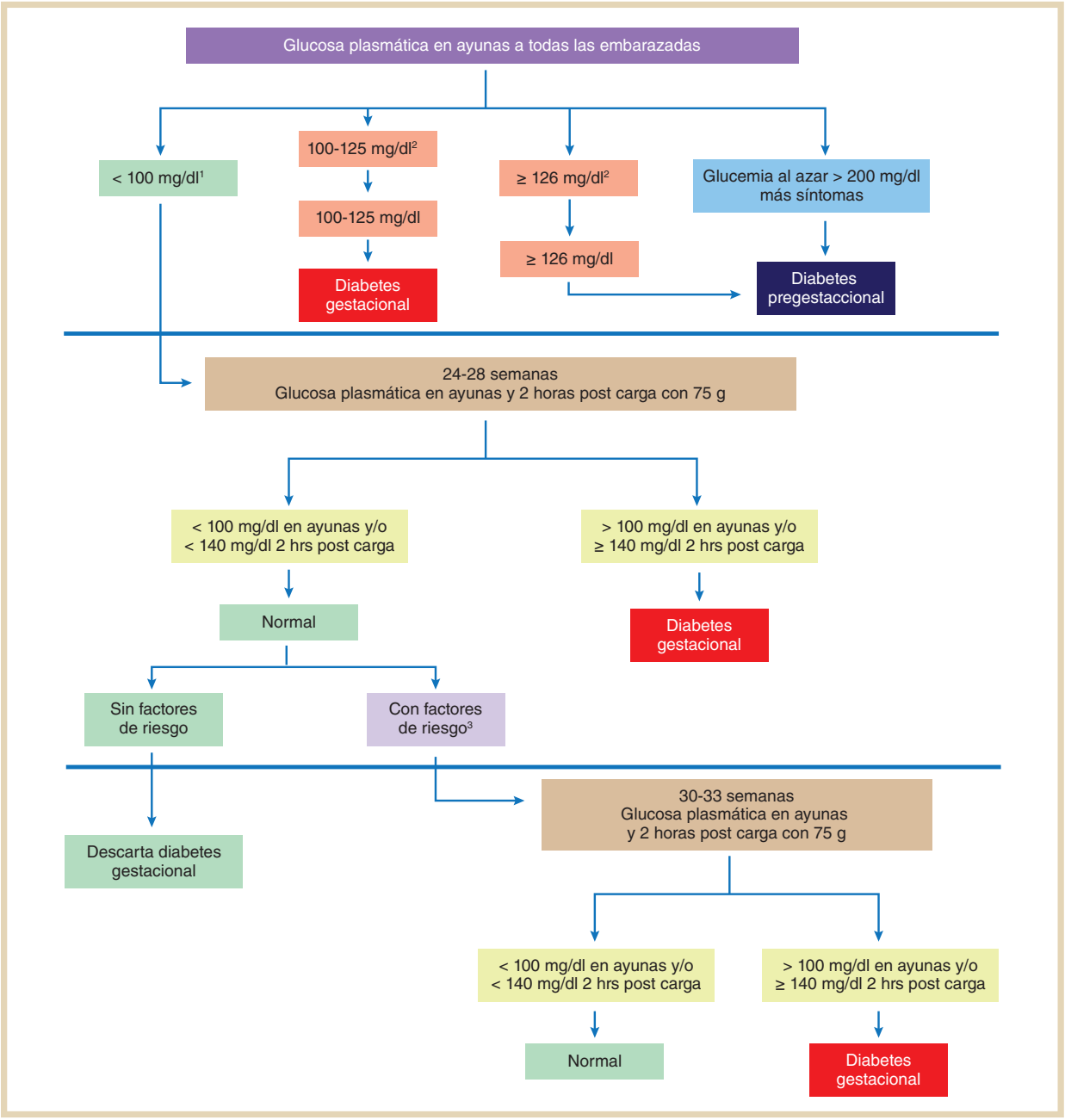

FIGURA 1. Algoritimo de diagnóstico de diabetes gestacional (adaptado de las guías de diabetes y embarazo del Ministerio de Salud del Gobierno de Chile, 2015) (1) Según criterio médico y dependiendo de los recursos sanitarios e institucionales, se recomienda que, en pacientes con varios factores de riesgo de alto impacto para desarrollo de DG y glucemia en ayunas normal, pedir una p75 al inicio para descartar una DPG no diagnosticada. En caso de resultar normal, seguir el algoritmo establecido (C). (2) Repetir glucemia sin restricción alimentaria en un plazo máximo de siete días.(3) Ideal: Retestear entre las 31 y 33 semanas a todas las embarazadas con factores de riesgo, priorizando a las embarazadas que presentan factores de riesgo aparecidos o desarrollados durante el embarazo.

Si bien el estudio HAPO se realizó entre las semanas 24 y 31, la IADPSG sugiere que el valor diagnóstico de ayunas (92 mg/dl) se aplique desde el primer trimestre. Por otro lado, se debe considerar el impacto psicológico negativo del diagnóstico durante el embarazo, por lo cual es importante evitar el sobrediagnóstico de esta entidad. Este criterio basa sus resultados y conclusiones sólo en el nivel de glucemia materno, y no considera otros factores que influyen en la macrosomía. Si bien la OMS en 2013 se adhirió a la recomendación de la IADPSG, aclara que la calidad de la evidencia es baja y la recomendación, débil (17).

Se recomienda realizar la detección a todas las embarazadas siguiendo el siguiente *algoritmo* (Fig. 1).

Cuándo iniciar la pesquisa de diabetes gestacional

La determinación de la glucemia en ayunas se debe realizar a toda mujer embarazada en la primer consulta prenatal. El algoritmo de diagnóstico se refiere a la población general de embarazadas (18). En casos particulares de pacientes con varios factores de riesgo de alto impacto podría solicitarse una p75 al inicio.

Los factores de riesgo para DG son (A):

– Edad ≥ a 30 años (19,20,21,22).

– Antecedentes de diabetes en familiares de primer grado (23,24).

– Obesidad (índice de masa corporal [IMC] ≥ 30 kg/m2) (25,26,2728).

– Glucemia en ayunas > 85 mg/dl (1,29).

– Antecedente de DG en embarazo anterior (30,31).

– Antecedentes de macrosomía en embarazo previo, peso al nacer > 4,000 g (32,33).

– Signos previos al embarazo de insulinorresistencia (34,35).

– Antecedentes de alto o bajo peso de la madre al nacer (> 4,000 o < 2,500 g) (36,37).

– Origen étnico con alta prevalencia de diabetes (21,38).

No existe evidencia suficiente para recomendar la determinación del índice Homeostasis *Model Assessment* (HOMA) en mujeres embarazadas.

Prevención de diabetes gestacional

Toda mujer embarazada obesa o con antecedente de DG, en especial si presenta glucemia en ayunas de 85-99 mg/dl en el primer control, debe tener un estricto seguimiento con plan de alimentación y actividad física, y sin intervención farmacológica, con el fin de prevenir el desarrollo de DG (39) (C).

Prueba de sobrecarga con glucosa 75 g (p75)

– La p75 se debe realizar por la mañana con 8 a 12 h de ayuno.

– Tres o más días previos a la prueba estar con dieta libre, con un mínimo de 150 g de hidratos de carbono/día y con actividad física habitual.

–Durante la prueba no se puede fumar ni ingerir alimentos y la paciente permanecerá en reposo.

No debe estar recibiendo fármacos que modifiquen la prueba (corticoides, β-adrenérgicos, etc.) ni cursando proceso infeccioso.

– Después de la extracción de una muestra de sangre en ayunas, la paciente ingerirá 75 g de glucosa anhidra disuelta en 375 cc de agua a temperatura

natural y deberá tomarla en un lapso de 5 min. A los 120 min del comienzo de la ingestión de la solución se volverá a extraer una muestra de sangre (40). Si bien algunas sociedades aceptan la prueba de 50 g de glucosa como tamizaje para DG (no para diagnóstico), este grupo de trabajo no recomienda la metodología en dos pasos. Se ha demostrado que la carga de 50 g no presenta una adecuada relación sensibilidad/ especificidad. La carga de glucosa óptima para el diagnóstico de DG es la de 75 g (41) (C).

Control y seguimiento

Objetivos de control metabólico. Monitoreo glucémico

El monitoreo glucémico es el parámetro de control metabólico más importante durante el embarazo, ya que permite tomar conductas terapéuticas rápidamente.

Su mayor utilidad se alcanza con educación y supervisión del cumplimiento. Los objetivos de control glucémico son:

– Glucemia en ayunas: entre 70 y 90 mg/dl.

– Glucemia 1 h posprandial: entre 85 y 140 mg/dl.

– Glucemia 2 h posprandial: entre 80 y 120 mg/dl.

Es fundamental, en forma conjunta, evitar las hipoglucemias

Uso de HbA1c y fructosamina como parámetro de control glucémico

El valor objetivo para la HbA1c durante el embarazo es controvertido. Algunos autores sostienen que deberían establecerse puntos de corte según la edad gestacional. La utilización de la HbA1c como herramienta de control en la DG se considera de poco valor, no sólo por el escaso tiempo de alteración de la tolerancia a la glucosa (pocas semanas), sino también porque son reducidos los niveles glucémicos que alcanza la paciente com DG. Se debe tener en cuenta que la HbA1c se modifica con la vida media del eritrocito, y ésta disminuye durante el embarazo normal debido a mayor hematopoyesis en respuesta a los niveles de eritropoyetina elevados, situación que también ocurre en la DG (41,42).

En relación con la fructosamina, un estudio realizado propuso como punto de corte para el primer trimestre un valor < 259 µmol/l; para el segundo trimestre, < 231 µmol/l, y para el tercero, < 221 µmol/l (43). Es de importancia tener en cuenta, entonces, que las proteínas glicadas no son el *gold standard*, al momento, como objetivo de control glucémico en el embarazo por variaciones que pueden encontrarse del método, como inter y intrasujeto, en diferentes momentos de la gestación. En síntesis, los parámetros de control considerados de referencia son: los valores del monitoreo glucémico y la ausencia de hipoglucemias (b).

Frecuencia del monitoreo glucémico

El esquema de automonitoreo glucémico (AMG) de la paciente con DG dependerá de la severidad de la alteración.

Según los recursos y el criterio médico, la indicación puede variar entre un mínimo de una glucemia capilar diaria, alternando mediciones en ayunas y posprandiales, hasta un esquema de indicación de AMG similar al de una paciente con DPG. Un control óptimo implica automonitoreos pre y posprandiales durante tres días, y luego se determinará la frecuencia y horarios según la terapéutica instituida y las necesidades de cada paciente. Es importante tener en cuenta que, en caso de curva de crecimiento ecográfico entre las semanas 28 y 30 con evidencia de un crecimiento disarmónico con una circunferencia abdominal mayor al percentil 70, se recomienda intensificar el monitoreo glucémico con el fin de evaluar escapes de hiperglucemia (45,46).

Control de cetonuria

Es importante realizar control de cetonas en orina en la primera orina de la mañana para evaluar la cetosis de ayuno, y si es positiva, modificar el plan de alimentación. Se recomienda también dosaje de cetonuria cuando el AMG sea ≥ 200 mg/dl en cualquier determinación del día o cuando la paciente presente descenso de peso (44) (B).

Tratamiento no farmacológicode la diabetes gestacional El tratamiento no farmacológico es aplicable tanto para la DG como para la DPG. Esto hace referencia a la educación y las medidas higiénico-dietéticas, las cuales, en caso de complicaciones como nefropatía o hipertensión arterial, se deberán adaptar a cada situación individual.

Educación

La educación puede ser individual en el transcurso de la consulta, durante la internación o en sesiones grupales. Es importante que se utilicen métodos y técnicas de participación activa que superen la charla informativa en un ambiente lúdico y contenedor. Los programas de educación terapéutica en embarazadas son una ayuda para aprender competencias básicas para el autocuidado de la enfermedad. Pero ¿qué competencias se deben desarrollar?:

– compender qué es la diabetes gestacional , sus alcances y la importancia del tratamiento.

– Si se inyecta insulina, conocer su efecto, saber dosificarla e inyectarla y conservarla correctamente.

– Saber interpretar y anotar los resultados de la glucemia capilar.

– Prevenir, actuar y saber en qué situaciones consultar al equipo médico cuando detecta una hiperglucemia y/o hipoglucemia.

– Integrar el tratamiento a su vida cotidiana de hábitos dietéticos, horarios y actividad habitual.

– Conocer la importancia de controles periódicos con su equipo médico y los diferentes especialistas.

– Prevenir en el futuro el desarrollo de DM2.

– Capacitarse en la lactancia materna y en la elección del método anticonceptivo.

– Elegir, junto al equipo profesional, la forma de terminación del embarazo (45)

Es muy importante evaluar las actividades educativas que se realizan, ya que tanto la evaluación inmediata como la tardía permiten mejorar las acciones planificadas. Se recomienda realizar educación terapéutica individual y grupal en mujeres con diabetes en el embarazo adaptada a las necesidades socioeconómicas y culturales de las mismas (45,46).

Plan de alimentación

En relación con el valor calórico total (VCT), durante el primer trimestre del embarazo se calcula según el peso teórico y la actividad física. A partir del segundo trimestre se le

agregan 300 kcal. Es necesario controlar el aumento de peso materno y ajustar el VCT según progresión y/o curva de peso maternofetal de forma personalizada. En caso de embarazadas con obesidad no es necesario adicionar calorías, pero se debe tener en cuenta que el VCT no debe ser menor de 1,600 kcal y no menos de 160 g de hidratos de carbono en el día de forma fraccionada.

En caso de embarazos múltiples:

– En embarazo gemelar es conveniente agregar 450 cal al VCT a partir del segundo trimestre y adecuar según la curva de peso.

– En embarazos de tres o más fetos se recomienda que el aporte extra de 450 cal al VCT se realice a partir del primer trimestre y hacer el seguimiento según la curva de peso materno y fetal.

En relación con el cloruro de sodio, no debe indicarse menos de 5 g por día (2 g de sodio/día). Se restringirá mínimamente en caso de hipertensión arterial crónica sensible a la sal o insuficiencia cardíaca (45,46,47). La distribución de las comidas se hará acorde a cada región. Se recomienda no superar un lapso de 6-8 h entre la última ingesta nocturna y el desayuno para evitar la cetosis de ayuno. En cuanto a las proteínas, en la práctica se recomienda agregar 10 g/día a partir del segundo trimestre.El 50% de la ingesta proteica diaria debe ser cubierta por proteínas de alto valor biológico (45). La ganancia de peso óptima del embarazo depende del IMC de la madre previo al embarazo (Fig. 2 y Tabla 3).

En relación con la ganancia de peso ritmo aconsejado de aumento es de aproximadamente 400 g/ semana a partir del segundo trimestre. En caso de un aumento superior a 500 g/ semana, evaluar posibles edemas. Se recomienda hacer seguimiento de peso con la curva de peso de Rosso- Mardones (47).

Actividad física

La actividad física resulta especialmente útil para ayudar al control metabólico en las gestantes con diabetes. Los ejercicios no isotónicos en los que predomina la actividad de las extremidades superiores serían los que menos afectarían al útero, con menor riesgo de desencadenar contracciones o de disminuir su oxigenación. Dado que hay mujeres que practican actividad física de forma regular antes del embarazo, es importante consultar al especialista e individualizar cada caso (48). Teniendo en cuenta lo hasta aquí mencionado, se sugiere contraindicar la actividad física en los siguientes casos:

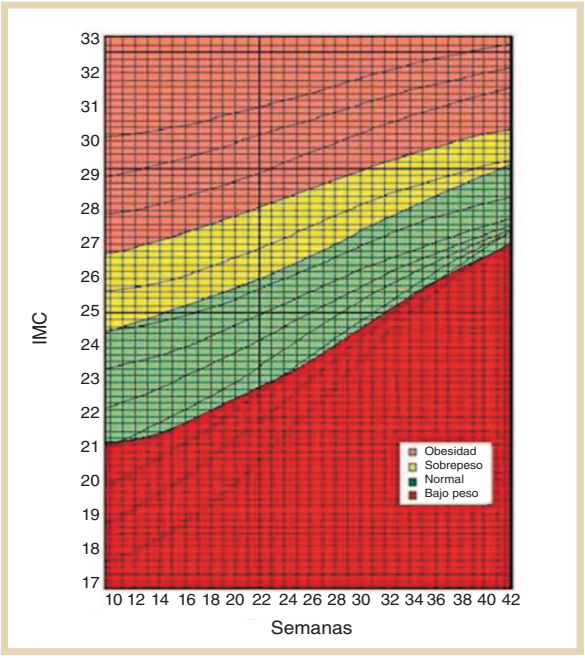

FIGURA 2. Incremento de peso según el IMC (adaptado de Calvo, et al.46).

TABLA 3. Ganancia de peso adecuada durante el embarazo

Estado nutricional previo (según IMC)	Ganancia de peso recomendada en todo el embarazo (kg)
Bajo peso (menos de 18.5)	12.5-18
Peso normal (18.5-24.9)	11-16
Sobrepeso (25-29.9)	7.0-11
Obesidad (≥ 30)	5-7

Adaptado de Rasmussen, et al.[45] y Calvo, et al.[46] (C).

– Cuando aumentan las contracciones uterinas.
– En caso de embarazo múltiple.
– Durante hipoglucemia o hiperglucemia con cetosis.
– Antecedente de infarto o arritmia.
– Hipertensión inducida por el embarazo.

Tratamiento farmacológico de la paciente con diabetes gestacional

El fármaco a utilizar con fundamento científico recomendado durante el embarazo es la insulina. En concordancia con este concepto, la ADA 2016 establece que la insulina es el agente de primera línea recomendado para el tratamiento de la DG (48) (A).

Insulinoterapia

La insulinoterapia es el tratamiento farmacológico de elección en la gestante con diabetes (A). Se indica en DG si después de siete días con tratamiento no farmacológico no se alcanzan los objetivos glucémicos en el 80% de los controles pre- y posprandiales solicitados. Si los valores glucémicos resultan muy elevados, se podrá abreviar dicho plazo o insulinizar desde el diagnóstico(50).

Tipo de insulina

Se sugiere utilizar insulina humana para reducir a su mínima expresión la formación de anticuerpos antiinsulina, ya que el uso de insulinas de origen animal (bovino, porcino) expone a la formación de los anticuerpos mencionados. Se recomienda iniciar la insulinoterapia con insulina *neutral protamine Hagedorn* (NPH) humana durante el embarazo por demostrar a día de hoy mayor evidencia científica a favor. Según los resultados de los AMG, se indicará NPH basal sola o con bolus de insulina rápida o ultrarrápida si fuera necesario (C). El uso del análogo detemir también fue aprobado por las entidades regulatorias para su utilización en el embarazo. Al respecto, el estudio de Mathiesen, et al. (49) encontró valores menores de glucosa plasmática en ayunas en la rama de detemir en comparación con las pacientes que estaban usando NPH humana. Al comparar ambos tipos de insulina, no se hallaron beneficios respecto a los resultados relacionados con el riesgo de hipoglucemias ni en los niveles de HbA1c. Consecuente a este estudio multicéntrico, el análogo detemir obtuvo la aprobación de la *Food andDrug Administration* (FDA) y otras entidades regulatorias (B) (50). El uso de glargina durante el embarazo no tiene aprobación. Se han reportado estudios observacionales retrospectivos con series muy pequeñas, donde se observa que la intervención fue efectiva para alcanzar el objetivo de control metabólico en siete pacientes y para reducir las hipoglucemias nocturnas en un caso. Estudios sobre toxicidad reproductiva no han mostrado efectos directos de la glargina sobre el desarrollo embrionario o fetal en animales (B, C) (50,51,52). Las insulinas de acción rápida o prandial que fueron aprobadas por las entidades regulatorias (FDA) son:

Insulina regular humana (categoría A para FDA) y análogo de insulina aspártica (categoría B) (53,54,55,56). Respecto al análogo lispro, en Argentina la Disposición 2510/12 de la

ANMAT establece que los datos sobre exposición de un gran número de embarazos no indican ningún efecto adverso en el feto ni en el recién nacido. Sin embargo, no se encuentra evidencia donde se hayan realizado estudios adecuados y bien controlados en mujeres embarazadas. Entonces, si bien este análogo de insulina (categoría B) se ha utilizado en estudios de cohorte con resultados satisfactorios y no se han observado efectos adversos en fertilidad ni en desarrollo embriofetal en animales, no está específicamente aprobado por no encontrarse estudios aleatorizados y controlados y adecuados (57).

Al respecto, es importante que cada país siga los lineamientos de las entidades regulatorias locales.

Indicación de insulina en diabetes gestacional

Se aconseja comenzar con 0.1-0.2 UI/kg de peso actual al día de insulina NPH o con insulinas prandiales (regular o análogos ultrarrápidos) con un esquema individualizado, según los AMG. Posteriormente, las dosis y el momento de aplicación se van ajustando según las necesidades propias de cada paciente (A, C) (50).

Antidiabéticos orales

Diversos estudios publicados sostienen la eficacia y la seguridad de la metformina (embarazo categoría B por FDA) y la glibenclamida (categoría B por FDA) para el tratamiento de la DG. La evidencia demuestra que ambos fármacos atraviesan la placenta y no existen, a día de hoy, datos de seguridad a largo plazo. La glibenclamida o gliburida ha sido utilizada por algunos grupos de investigadores, pero se debe tener en cuenta que está asociada a mayor hipoglucemia en el recién nacido, entre otras complicaciones (58). El uso de metformina durante el embarazo para el tratamiento de la DG es aún discutido. En relación con el síndrome de ovarios poliquísticos en tratamiento con metformina, se puede continuar hasta la semana 20 de embarazo o primer trimestre de gestación (58,59). En síntesis, el grupo de trabajo evita recomendar fármacos que no estén aprobados por las entidades regulatorias para su utilización en el embarazo, como es el caso de estos dos agentes orales.

Frecuencia en el control y seguimiento de la paciente con diabetes gestacional

Dependerá del esquema terapéutico y la evolución de la paciente o la respuesta terapéutica a la intervención, la presencia de complicaciones del embarazo y el sistema local de salud. En mujeres con DG menores de 25 años, sin antecedentes familiares de diabetes, con peso normal o bajo peso y que presenten diabetes antes de la semana 20 de gestación se podrían dosificar anticuerpos anti-GAD y ZnT8 para identificar diabetes de tipo autoinmune. En caso de no acceder al dosaje de los mencionados anticuerpos, en dicha etapa de la gestación se podría considerar realizar finalizada la gestación en el momento de la reclasificación (60). En mujeres menores de 25 años, sin signos clínicos de DM2 ni antecedentes familiares de diabetes en varias generaciones se sugiere, dentro de la accesibilidad, realizar estudio genético para descartar diabetes de tipo *Maturity Onset Diabetes of the Youn*g (MODY) (61).

Reclasificación posparto

Se recomienda realizar glucosa plasmática en ayunas por laboratorio, con dieta libre, antes del alta en toda diabética gestacional para descartar presencia de DM (2 glucemias ≥ 126) mg/dl) (62).

Reclasificación a la sexta semana posparto

En toda paciente con glucemias en ayunas normales durante el puerperio, se deberá realizar una evaluación del metabolismo hidrocarbonado. Se recomienda realizar una p75 según la metodología de la OMS para definir el estado metabólico glucémico en el posparto (Fig. 3).

Se sugiere repetir la prueba anualmente e incluirlas en un programa de prevención de diabetes (62,63). Se deberá anticipar la valoración del metabolismo de la glucosa cada vez que exista sospecha clínica de diabetes.

Anticoncepción

En mujeres con antecedentes de DG no existe contraindicación específica para el uso de anticonceptivos, por lo que la elec ción deberá estar basada en las preferencias de la pareja, teniendo en cuenta los criterios de elegibilidad establecidos por la OMS (64) (C).

CONCLUSIÓN

Este grupo de trabajo no acepta adherirse a la propuesta de diagnóstico de la IADPSG, ya que incrementa significativamente la prevalencia de DG y con ello los recursos. A su vez, a día de hoy no se encontró evidencia respecto a la mejora de los resultados. Los criterios recomendados por la ALAD se encuentran avalados por el análisis de impacto de los diferentes criterios diagnósticos realizados en el Reino Unido (65).

Se considera que en Latinoamérica la obesidad constituye gran parte del problema, siendo entonces la propuesta continuar con el criterio diagnóstico ALAD 2007 e invertir recursos en mejorar el estado nutricional de las mujeres en edad reproductiva antes del embarazo.

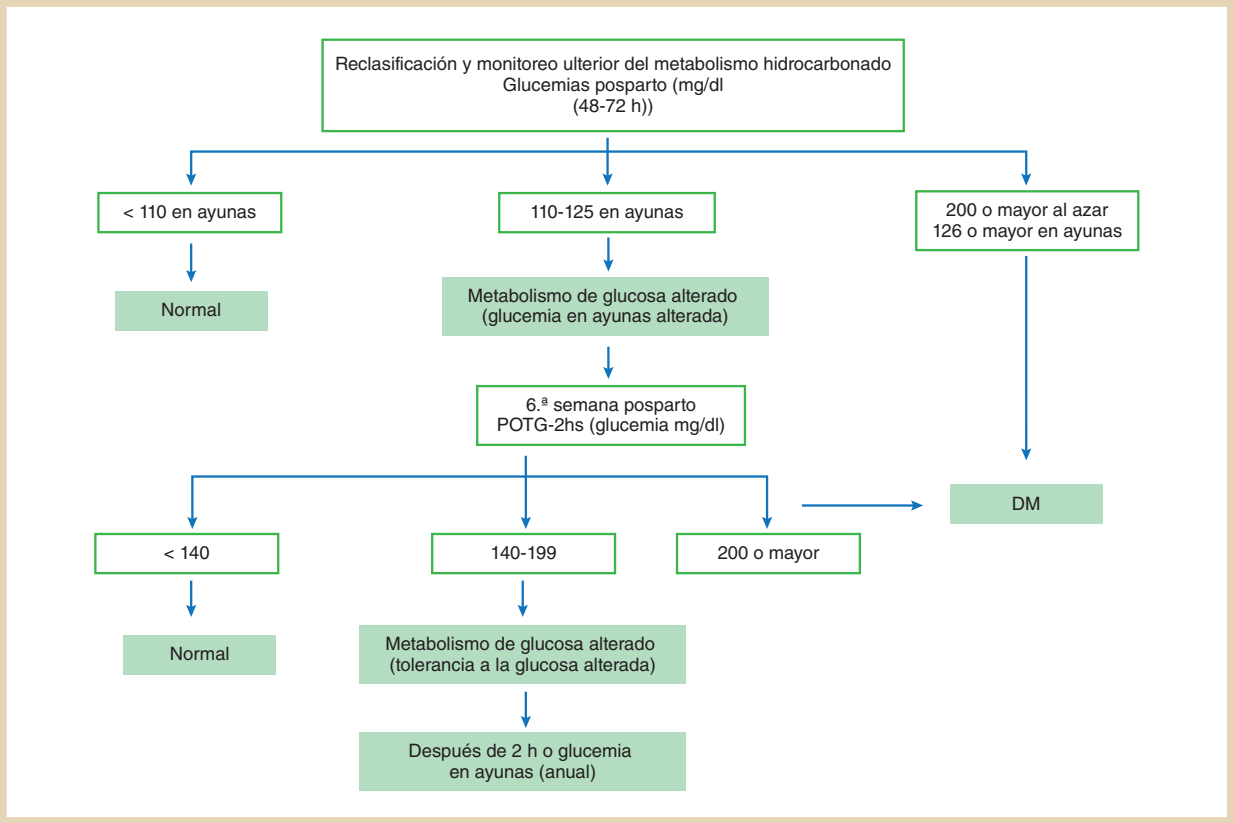

FIGURA 3. Algoritmo de reclasificación y monitoreo ulterior del metabolismo hidrocarbonado (adaptado de las guías NICE, 2015).

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ORIGINAL ARTICLE
TOPICS IN MEDICAL CLINIC
ADHERENCE TO OSTEOPOROSIS TREATMENT – A STUDY IN PATIENTS FROM A UNIVERSITY HOSPITAL

ADERENCIA AO TRATAMENTO DA OSTEOPOROSE: UM ESTUDO EM UM HOSPITAL UNIVERSITÁRIO.

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Key words: Osteoporosis, Fracture, Medication adherence
Descritores: Osteoporose, Fratura, Aderência a medicação

Abstract

Background: Good adherence to osteoporosis (OP) treatment is very important to prevent low impact fractures. Patients survival may also be affected. **Aim:** To study adherence to anti-osteoporotic treatment in our region and the possible determinants of the non-adherence. **Methods:** Ninety eight patients from a single university Hospital were interviewed using the Morisky-Green-Levine questionnaire that is an instrument to evaluate the adherence to a treatment and with the International Physical Activity Questionnaire (IPAQ) that evaluates the regular practice of physical exercises. Epidemiological, social and clinical data were extracted from the charts and through direct questioning. **Results:** Only 18.3% of patients had a good adherence. Most of them did not have a satisfactory level of physical exercises (59. 1%). Only African ethnic background seems to be associated with treatment low adherence (p=0.009). All the others studied variables (caregiver presence, educational level, presence of previous fracture, number of comorbidities and ingested daily pills as well as age and medication gratuity) did not associate with the degree of adherence (all P=ns). **Conclusions:** There is a very low adherence to osteoporosis treatment in our region. Afrodescentants have a lower adherence than Caucasians. **Endocrinol diabetes clin exp 2017 2002 -2005.**

Resumo

Justificativa: Boa aderência ao tratamento de osteoporose é fundamental para que se evitem as fraturas de baixo impacto. A sobrevida do paciente também pode ficar afetada. **Objetivo:** Estudar o grau de aderência ao tratamento de osteoporose em nossa região e determinar os possíveis fatores que influem na não aderência. **Métodos:** Foram estudados 98 pacientes de um único Hospital Universitário os quais foram entrevistados usando-se o questionário de Morisky-Green-Levine – que é um questionário para avaliação de aderência ao tratamento e o Questionário internacional de atividade física- o qual avalia a prática de atividades físicas. Dados epidemiológicos, sociais e clínicos foram extraídos dos prontuários e por questionamento direto. **Resultados:** Somente 18.3% dos pacientes apresentavam uma boa aderência ao tratamento. A maioria deles não praticava atividades físicas de maneira satisfatória (59.1%). Somente a etnia afrodescendente esteve associada coma má aderência (p=0.0009). Todas as outras variáveis estudadas (presença de cuidador, nível de educação, presença de fraturas prévias, número de comorbidades e de pílulas ingeridas/dia assim como idade e gratuidade da medicação) não estiveram associadas ao nível de aderência (todos com p=ns). **Conclusão:** Existe uma aderência muito baixa ao tratamento da osteoporose em nossa região. Afrodescendentes têm um a pior aderência do que caucasianos. **Endocrinol diabetes clin exp 2017 2002 -2005.**

INTRODUCTION

Osteoporosis (OP) is a systemic skeletal disease characterized by reducing bone mass and microarchitectural deterioration of the bone tissue. It increases bone fragility raising the fracture risk (1).

Risk factors for osteoporotic fracture comprise older age, female sex, postmenopause for women, hypogonadism or premature ovarian failure, low body weight, past of parental hip fracture, ethnic background (Caucasians and Asians are at highest risk), former vertebral fracture or fracture due to minimal trauma. Also are risk factors: rheumatoid arthritis, smoking, alcohol intake, low calcium diet, vitamin D deficiency, immobilization and use of some medications such as steroids, anticoagulants, anticonvulsants and cancer drugs (1).

OP is found in estimated 200 million people worldwide (1), and an estimated 54 million men and women in the United States have osteoporosis or low bone density (1). About 50% of Americans older than 50 years are at risk for osteoporotic fracture (1). The economic burden of this disease on the health care system is projected to be $25.3 billion per year by 2025 (1).

OP treatment is fundamental to lower the risk of fractures. It is done with traditional measures such as exercises, dietary and supplemental calcium, and vitamin D and drugs that prevent drug reabsorption or favor bone formation (1,2). OP pharmacologic treatment includes bisphosphonates, teriparatide, calcitonin, estrogen and selective estrogen receptor modulators (SERMs) and denosumab.

The first choice is usually oral bisphosphonates, with parenteral medications reserved for intolerance to the oral medications (2). The decision to prescribe any of this medication depends on the efficacy and side effects (2). There is also the responsibility to use these medications in a cost effective manner. Non-adherence to therapy can reduce its beneficial effects (3) and consequently its effectiveness (3) and the non-adherence percentage has been estimated to be as high as 50% in chronic diseases (3).

The aim of this study was to determine the adherence to anti-osteoporotic treatment in our region and the possible determinants of the non-adherence.

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MATERIAL AND METHODS

This study was approved by the local Committee of Ethics in Research and all participants signed consent. A sample of 98 patients (5 males and 93 females) with mean age of 69.10±8.33 years old and a median time of OP diagnosis of 6 years (3 to 10 years) were studied for epidemiological and educational profile, data on coexistence of depression and fibromyalgia, number of pills/daily, presence of caregiver, source of used medications and use of measures to avoid falls. Charts were reviewed for densitometry (by DEXA) results and history of previous low impact fractures. All patients were submitted to a Morisky-Green--Levine questionnaire (4) that is an instrument to evaluate the adherence to a treatment and that has four questions allowing to classify the patients in adherent, with moderate adhesion and non-adherent (4). It was also applied the International Physical Activity Questionnaire (IPAQ) that evaluates the regular practice of physical exercises and classifies patients in sedentary, insufficiently active, active and very active according to duration, frequency and type of physical activities (5) . All used instrument were translated to Portuguese language (4,6). All studied patients were on oral bisphosphonate therapy.

Data was collected in contingency and frequency tables. Comparison of nominal data was done by chi squared test. Numeric data was compared by Kruskall Wallis and one way Anova. The adopted significance was of 5%.

RESULTS

The analysis of the sample showed that 75/98 (76.5%) were Caucasians and 23/98 (23.4%) were Afro descendants. The hip T score varied from -4.5 to 0.5 (mean 1.932±0.872) and the Lumbar spine T score from -5.8 a -2,0 (mean of -2.557±1.090). These patients had the presence of 1 to 7 comorbidities (median of 3) with depression in 15/98 (15.3%) and fibromyalgia in 22;/98 (22.4%). They ingested from 1 to 15 pills a day (median of 6) and 22/97 (22.6%) had a care giver. The used medication was freely distributed by the National Health System (SUS) in 68/95 (71.5%). The study of educational profile showed that 11/98 (11.2%) never studied, 61/98 (62.2%) had first degree, 25/98 (36.7%) had the second degree and 1/98 (1.02%) had superior degree.

In the studied sample only 18/98 (18.3%) was considered adherent to the drug treatment. Moderate adhesion was observed in 61/98 (62.2%) and low adherence in 19/98 (19.3%). Concerning physical activity: 18/98 (18.3%) were sedentary; 40/98 (40.8%) were insufficiently active, 35/98 (35.7%) active and 5/98 (5.1%) were very active.

The comparison of studied variables according to the degree of treatment adhesion is on **table 1**.

Table 1. Comparison of Epidemiological and Social Profile of Patients with Low, Moderate and Good Adherence to Osteoporosis Treatment.(N=98)

	Low N=19	Moderate N=61	Good N=18	p
Female gender	19/19-100%	57/61 -93.4%	17/18 – 94.4%	0.52
Mean Age (years)	67.1±7.98	68.7±8.01	72.4±9.21	0.13
Mean disease duration (years)	6.2±7.9	8.8±7.5	6.9±4.05	0.31
Ethnic background	C=10/19 -52.6% A=9/19- 47.3%	C=48 /61=78.6% A=13/61= 21.3%	C= 17/18 -94.4% A=1/18= 5.5%	**0.009**
Caregiver presence	6/19 -31.5%	12/61 =19.6%	4/18 =22.2%	0.55
Formal study	None=2/19 1st degree=15 2nd degree =2	None=8/61 1st degree =36/61 2nd degree= 16/61 Superior 1/61	None=1/18 1st degree = 10/18 2nd degree=7/18	0.49
Low impact fractures	2/19 -10.5%	6/61 -9.8%	4/18 -22.2	0.35
Measures to avoid fall	11/19 -57.8%	23/61	10/18	0.21

Physical Activities	Sedentary = 6/19 Insufficient=7/19 Active =4/19 Very active =2/19	Sedentary =7/61 Insufficient =26/61 Active= 26/61 Very active =2/61	Sedentary = 5/18 Insufficient= 7/18 Active=5/18 Very active =1/18	0.22
Median number pill/day	6 (5-8)	6 (4-7.5)	6 (5-8)	0.33
Median number of co morbidities	3 (2-5)	3 (2-4)	3.5 (2-4.2)	0.53
Depressuion	3/19 – 15.7%	10/61 -16.3%	2/18=11.1%	0.85
Fibromyalgia	6/19 -31.5%	12/61 =19.2%	4/18 =22.2%	0.55
Median T score - hip	-1.7 (-2.5—1.2)	-2.1(-2.4 to -1.5)	-2 (-2.7 to -1.4)	0.56
Median T score - spine	-2.15 (-3.2 to -1.75)	-2.7(-3.2 to -2)	-2.5 (-3.45 to -2.02)	0.48
Free medication	13/19	41/59	14/18	0.76

A= Afro descendants; C= Caucasians; SUS- National health care.

DISCUSSION

Our results showed that there is a very low adherence to osteoporosis treatment of our region, considered to be good in only 18.3% of patients. Also, most of them did not had a satisfactory level of physical exercises (as sedentary individuals plus those with insufficient activities were almost 60% of the sample). Having a previous fracture, a caregiver or depression did not influence its use, neither number of comorbidities, educational level and previous low impact fracture. Only African background – that in our region is, unluckily, a surrogate for lower economic income – was associated with lower adherence.

Osteoporotic fractures are a serious health problem that can cause severe pain and have been associated with an increased mortality rate (3). Anti-osteoporotic therapy has been reported to reduce mortality in those at high risk of fractures (7-9). A revision by Siris et al (10) showed that those who obey to the treatment had a 37% reduction in the risk of hip or vertebral fractures , while according to Cramer et al(11) those who were not compliant had a higher risk of fractures and a higher risk of vertebral and hip fractures. So improving compliance to anti-osteoporotic medication is vital, and this may be achieved through improved orientations at clinical consultation with patients education and follow-up monitoring.

Another study, in Santa Catarina, Brazil (12), has showed a rate of non-adherence lower than ours, of 53.8% and some of the main reasons given to it was to forget to take the medication, lack of care with the time to take the medication as well as feeling bad when take the drugs. Roh et al (13) in a study of 116 osteoporotic females with distal radius fracture found that the most important factor in treatment adherence were health literacy, adverse drug events, or presence of medical comorbidities. A recent analysis in the rural area in Netherlands (14) found that patients older age and the general practitioner prescribing the majority of medication were associated with better adherence and persistence. They also found that good adherence in the first prescription year was associated with better persistence (14).

Medications prescribed to patients with osteoporosis usually need to be taken for several years in order to achieve successful outcomes, in particular the prevention of osteoporotic fractures (15,17). Consequently, lack of patient compliance, persistence, and adherence precludes its beneficial effects.

This study has the limitations of having a small sample and a cross-sectional design. However it does highlight the need for vigorous measures to improve treatment compliance of osteoporosis patients in order to achieve fracture prevention.

CONCLUSION

We concluded that there is a very poor compliance to osteoporosis treatment in our region. The doctors who attend these patients must act energetically in order to improve the adherence to avoid fractures and improve patient's survival.

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ORIGINAL ARTICLE
TOPICS IN MEDICAL CLINIC
NEUTROPHIL -TO - LYMPHOCYTE RATIO (NLR) AND DISEASE ACTIVITY IN RHEUMATOID ARTHRITIS

RELAÇÃO NEUTROFILOS/LINFOCITOS E ATIVIDADE DE DOENÇA EM ARTRITE REUMATOIDE.

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Key words: Osteoporosis, Fracture, Medication adherence
Descritores: Osteoporose, Fratura, Aderência a medicação

Abstract

Justificativa: Alguns autores descrevem que a medida da relação neutrófilo/linfócito (NLR) pode ser útil na determinação de atividade inflamatória na Artrite reumatoide (AR). **Objetivo:** Estudar a correlação entre atividade da AR medida pela VHS (velocidade de hemossedimentação), PCR (proteína C reativa) DAS (Disease activity score) 28-VHS e DAS28-PCR. **Métodos:** Foram estudados 209 pacientes com AR (9.5% homens, 89.9% mulheres , coim díade média de 55.1±11.1 anos) de um único ambulatório de Reumatologia para NLR, dados epidemiológicos, clínicos e de atividade de doença: VHS, PCR, DAS28 ESR e DAS28 PCR. **Resultados:** Não foi possível notar correlação entre NLR e VHS, DAS 28-VHS, DAS 28-CRP . Na análise univariada existia correlação da NLR com a PCR (p=0,03), associação esta que foi perdida quando se fez a correção para idade, gênero, índice de massa corporal, fumo e uso de prednisona (p=0.10). Todavia observou-se uma associação entre menor NLR com uso de biológicos (p= 0.002) **Conclusões:** Não foi possível demonstrar associação a NLR com atividade da AR na presente amostra. Observou-se associação de menor NLR com uso de drogas biológicas. **Endocrinol diabetes clin exp 2017 2006 -2009.**

Abstract

Background: Some authors have described that measurement of the neutrophil / lymphocyte ratio (NLR) may be useful in the determination of inflammatory activity in rheumatoid arthritis (RA). **Objective:** To study the correlation between RA activity measured by ESR (erythrocyte sedimentation rate), CRP (C--reactive protein) DAS 28-ESR and DAS28-CRP. **Methods:** Twenty-nine patients with RA (9.5% men, 89.9% women, mean age 55.1 ± 11.1 years) from a single Rheumatology outpatient clinic were studied for NLR, epidemiological, clinical and disease activity data: ESR, PCR, DAS28-ESR and DAS28-CRP. **Results:** It was not possible to observe correlation between NLR and ESR, DAS 28-ESR, DAS 28-CRP. In the univariate analysis, there was a correlation between the NLR and the CRP (p = 0.03), which was lost when corrected for age, gender, body mass index, smoking and prednisone use (p = 0.10). However, there was an association between lower NLR with use of biological drugs (p = 0.002). **Conclusions:** It was not possible to demonstrate the association of NLR with RA activity in the present sample. An association of lower NLR with use of biological drugs was observed. **Endocrinol diabetes clin exp 2017 2006 -2009.**

INTRODUCTION

Rheumatoid arthritis (RA) is an inflammatory disease that causes articular damage if patients are not properly treated (1,2). To treat correctly a RA patient it is necessary to properly access disease activity. However, no single measure is considered good to do it. So composite instruments have been used such as the 28-joint Disease Activity Score (DAS28), the Simplified Disease Activity Index, and the Clinical Disease Activity Index (1,2).

Patients with RA have frequently shown neutrophilia and lymphopenia. While neutrophilia is triggered by systemic inflammation, the pathogenesis of lymphopenia is uncertain (3). Neutrophil-to-lymphocyte ratio (NLR) have been presented as easily measured, and low-cost indicators to define inflammation (3). Neutrophil- to-lymphocyte ratio has also been found to be associated with different types of malignancies, metabolic syndrome, infectious diseases, cardio vascular disease, end stage renal disease and other inflammatory diseases. (4-10)

In the present research, we studied NLR in RA patients to see if it is associated with other inflammatory markers such as ESR (erythrocyte sedimentation rate), CRP (C reactive protein) and DAS 28.

MATERIAL AND METHODS

This is a retrospective study that was approved by the Local Committee of Ethics in Research . We included 209 RA patients with at least four classification criteria for Rheumatoid Arthritis diagnosis from American College of Rheumatology/ European League Against Rheumatism (ACR/EULAR)2010 (11) that come for regular consultations in the period of one year in the Rheumatology Outpatient Clinic of a University Hospital. Clinical and epidemiological were collected from charts. Data on ESR, CRP, NLR, DAS 28 ESR and Das28 CRP, were calculated with data from the last visit(2). Clinical and epidemiological included: gender, age, disease duration, tobacco exposure, body mass index (BMI) presence of rheumatoid factor and nodules as well as used treatment.

Results were collected in frequency and contingency tables. TO compare NLR according to nominal variables, the unpaired t test and Mann Whitney testes were used. Correlations studied were done by Spearman Test. Multiple regression was used to study NLR in relation to inflammatory tests (DAS28 ESR, DAS28 CRP, ESR and CRP) with correction for gender, age, BMI, ethnic background and glucocorticoid use. The significance adopted was of 5%. Calculations were done using the software Medcalc 10.0.

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RESULTS

The sample had 21/209 (9.5%) males and 188/209 (89.9%) females with age from 19 to 81 years (mean 55.1±11.1 years); median disease duration of 10 years (range 1,0 to 47 years); 76.4% were Caucasians; 22.6% were afro descendants; 62.1% had positive rheumatoid factor and 11.3% had rheumatoid nodules. About 41.07% have been exposed to tobacco (current and previous smokers) and 26.7% were present smokers. The BMI varied from 17.8 to 51.8 kg/m2 (median value of 27.2 kg/m2); the ESR from 1.0 to 100.0 mm (median value of 34.5mm), the CRP from 0 to 96 mg/dL (median value of 6.0 mg/dL); DAS28 ESR from 0.49 to 8.07 (median 3.49), the DAS28 CRP from 1.04 to 7.26 (median value of 3.0). In this sample 73.9% were using methotrexate; 63.7% were using glucocorticoid (doses from 5mg to 20 mg/day); 49,4% were on leflunomide and 28.5% were on biologics (84.7% on anti TNF; 4,3% on anti CD20; 15,2% on abatacept).

The NLR varied from 0.31 to 10.87 (median value of 2,02) and the hemoglobin value from 7.6 to 16.2 g/dL (median value of 12.9 g/dL)

Table 1 shows the association studies of NLR with the numerical variables. There it is possible to see that the found correlation was with C reactive protein

Table 1. Correlation studies of neutrophil-to-lymphocyte ratio (NLR) with epidemiological data and inflammatory markers in Rheumatoid arthritis patients.

	Rho	95% confidence interval	p
ESR (erythrocyte sedimentation rate)	0.01	-0.12 to +0.14	0.86
CRP (C reactive protein)	0.15	0.008 to 0.28	**0.03**
DAS (disease activity score)28 ESR	0.03	-0.09 to +0.17	0.57
DAS CRP	-0.05	-0.22 to +0.12	0.56
Age (years)	-0.08	-0.23 to +0.05	0.22
Age at disease onset	0.005	-0.15 to +0.16	0.94
Disease duration	0.12	-0.03 to +0.27	0.11
Glucocorticoid dose	0.07	-0.117 to 0.26	0.44
Body mass index	-0.05	-0.20 to -0.09	0.50
Hemoglobine	-0.04	-0.18 to+0.09	0.50

Table 2 shows the comparison of NLR according to numerical variables studied. Female gender patients had lower NLR than males as well as biologic drugs users.

Table 2. Comparison of neutrophil-to-lymphocyte ratio (NLR) according to the numerical variables studied.

	With the variable	Without the variable	P
Female gender	0.31-10.50 Median 1.93 (1.30-2.75)	1.16-10.88 Median 2.31 (1.66-4.42)	0.02
Caucasian ethnic background	0.95-8.90 Median 2.11 (1.55-2.85)	0.42-10.8 Median 2.06 (1.42-2.79)	0.51
Positive rheumatoid factor	0.65-10.8 Median 2.11 (1.45-2.96)	0.42-8.90 Median 1.95 (1.30-2.67)	0.35

Rheumatoid Nodules	0.65-10.88 Median 2.21 (1.57-4.37)	0.42-10.67 Median 2.03 (1.43-2.88)	0.32
Tobacco exposed	0.42-10.88 Median 2.21 (1.51-3.01)	0.65-8.90 Median 1.86 (1.42-2.74)	0.19
Current smokers	0.85-10.8 Median 2.24 (1.59-3.00)	0.42-10.6 Median 1.96 (1.43-2.88)	0.18
Glucocorticoid users	0.31-10.50 Median 2.06 (1.43-2.75)	0.41-10.8 Median 2.03 (1.32-2.99)	0.84
Methotrexate users	0.31-10.8 Median 2.06 (1.43-2.90)	0.42-6.15 Median 2.03 (1.37-2.74)	0.59
Leflunomide users	0.31-10.88 Median 2.10 (1.41-2.74)	0.42-10.5 Median 2.03 (1.42-2.88)	0.97
Biologic drugs users.	0.31- 8.9 Median 1.67 (1.03-2.71)	0.41-10.88 Median 2.11 (1.49-2.94)	**0.002**

When the correlations of inflammatory markers with NLR were studied with correction for age, gender, BMI, ethnic background, current tobacco and glucocorticoid use, no positive correlation was found : DAS 28 ESR (p=0.28); DAS 28 CRP (p =0.24), CRP levels (p=0.10), and ESR levels (p =0.38).

DISCUSSION

Systemic inflammation is related with neutrophilia, thrombocytosis, lymphopenia, and normochromic anemia (3). Consequently, the features of circulating blood cell components have been proposed to be biomarkers for evaluation of inflammatory activity (3). The neutrophil-to-lymphocyte ratio (NLR) is the proportion of absolute neutrophil count to lymphocytes on routine complete blood count (CBC) tests. There have been a number of studies regarding the NLR as a marker of inflammation (4,5,6,7,8,9,10).

One study has established that lymphopenia is present in 15% of patients with RA despite fluctuations in disease activity and that this is due to fewer circulating T-cell despite a normal number of circulating B-cells (12). Fewer T-cells might be circulating because they gain access to the synovial membrane, which is the main pathogenic focus of RA (12). Despite the fact that Chandrashekara et al (3) found that in RA adult patients, NLR have a good correspondence with CRP, and DAS CRP but we could not prove this last association. We only found correlation of NLR with CRP in univariate analysis. CRP is a nonspecific inflammatory marker that may be affected by several other factors including patients BMI, tobacco exposure, age, etc. When the correction was done for possible intervenient factor this correlation was lost. Also, the NLR is influenced by several conditions including medication, dehydration, overhydration, diluted blood specimens, and in vitro specimen handling (13-15). So conditions that are related to NLR levels should be kept in mind when NLR levels are interpreted. Probably, NLR as a nonspecific marker of disease activity, suffers influence of multiple variables and may not be reliable in reflecting the inflammation in one type of disease.

An interesting finding in the present study was that the use of biologic drugs was associated with lower NLR. This result is according to those of Koiwa et al (16) that noted that RA patients when treated with biological drugs showed significant decrease in their NLR. NLR has been also used as a predictor of response to chemotherapy and radiotheraphy in cancer patients (17,18).

Seo et al (19) studying the NLR in adult onset Still diseases (AOSD) concluded that the NLR did not differ according to the presence or absence of clinical manifestations, such as skin rash or sore throat and that the NLR was not a good marker for evaluation of disease activity in patients with AOSD although it could be used as a diagnostic tool and to predict disease relapse.

CONCLUSION

Concluding, we could not find any association of NLR with disease activity in RA in the present study but we have noted a lower ratio in patients using biological drugs. More studies with a prospective design are needed to further clarify this issue.

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CASE REPORT
GENDER DYSPHORIA: HOW TO APROACH?

DISFORIA DE GÊNERO: COMO ABORDAR?

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Key words: Gender dysphoria, Transgender, Transsexuality
Descritores: Disforia de gênero, Transgênero, Transexualidade

Abstract

Gender dysphoria is a subject that has been more frequently studied recently, with several studies of significant impact showing the importance of proper ways to diagnose and manage such cases in order to achieve better mental and physical health of transgender subjects. The lack of knowledge of general population, intolerance and prejudice result in increased mortality rates in the transgender population, who are victims of self and hetero aggressiveness. A multidisciplinary approach to transgender patients is of fundamental importance to improve biopsychosocial evaluation of patients and to achieve treatment success. **Endocrinol diabetes clin exp 2017 2010 -2012.**

Resumo

A disforia de gênero é um tema que atualmente vem sendo abordado com maior frequência, com muitos estudos de impacto mostrando a importância do correto diagnóstico e manejo para a saúde mental e física dos indivíduos transexuais. A falta de conhecimento da população em geral e a intolerância e preconceito resultam em uma elevada taxa de mortalidade nesta população de indivíduos, vítimas de auto e heteroagressividade. A abordagem multidisciplinar do paciente transgênero é de fundamental importância para que o paciente seja avaliado no âmbito biopsicossocial e o tratamento tenha êxito. **Endocrinol diabetes clin exp 2017 2010 -2012.**

INTRODUCTION

Physiopathology of gender dysphoria is not well comprehended and seems to be involved with multiple factors of genetic, anatomic and environmental order beyond others. Transgender individuals show signs of incongruence between their gender role determined by society according to their biological sex and their gender identity (1,2,3). The purpose of this case study is to describe the case of a transgender patient attended by our service of endocrinology and to contribute to developing quality standards for patient approach from diagnostic to hormonal treatment and clinical monitoring.

CASE REPORT

M.B.S, 34 years old, male transgender, menarched at 9 years old, 63 inches tall, and 194lb of weight and body max index (BMI) of 34 kg/m2 was sent to the Ambulatory of Endocrinology of the Hospital Evangélico of Curitiba with the intention of weight loss. The patient did not show other comorbidities and was subjected to abdominoplasty surgery after losing 66 pounds. Despite the reason for the appointment, it was identified an indiscriminate use of intramuscular testosterone propionate for a one year period (200 mg/ml), when it was prescribed 1 ml every 4 days in association with 75 mcg of Gestodene and 30 mcg of Ethinylestradiol which was prescribed for daily oral administration. On the physical exam, there were observed signs of virilization as low tone of voice, increased facial hair and incipient alopecia of androgenetic pattern, without other alterations.

Although there was an orientation about the indiscriminate use of testosterone, the patient showed reluctance to discontinue his conduction. He was assigned to interdisciplinary follow-up with services of psychology, gynecology, nutrition and a three-month follow-up appointment at the endocrinology service with laboratory exams to reevaluate comorbidities and lifestyle.

The patient only returned to the endocrinology ambulatory after one year and a half. He showed an increase in BMI (38,3 kg/m2) and did not do the prescribed exams nor the interdisciplinary follow-up that was proposed. During the period between appointments, he was submitted to mammoplasty reduction by his own desire and substituted his estrogen-progestin contraceptive by 50 mg/ml of Medroxyprogesterone Acetate (intramuscular). After receiving orientations about the possibilities of hormone therapy, its risks, its benefits and expected body changes, he interrupted the indiscriminate use of Testosterone Propionate, showing interest in adhering to the treatment proposed by the doctors. Blood exams were asked once again as well as interdisciplinary approach with a three-month follow-up appointment.

The patient returned to service with the laboratory exams referred in TABLE 1. There were no significant changes regarding clinical exam except by the increase of BMI (39,2 kg/m2). It was decided to start with testosterone undecanoate 1000 mg every 3 months and Metformin 1g per day according to dysglycemia

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Table 1. Laboratory evaluation

Parameters (units)			
HCT (%)	HB (g/dl)	39%	13,5
White blood cells (cells/mm3)		5650	
Urea/creatinine (mg/dl)		23/ 1,06	
Sodium(mmol/L)		138	
Potássium (mmol/L)		4,3	
Total calcium (mg/dl)		10,2	
Vitamin B12 (pg/ml)		401,9	
Albumin (g/dl)		4,23	
25(OH)D (ng/ml)		32,72	
Fasting glucose (mg/dl)		115	
Total cholesterol (mg/dl)		221	
HDL (mg/dl)		85	
TG (mg/dl)		76	
LDL (mg/dl)		120	
AST (U/L)		30	
ALT (U/L)		32	
CK (U/L)		155,5	
TSH (mU/L)		0,87	
Free T4(ng/dL)		0,82	
CA 125		26,95	
Beta-HCG (U/ml)		<25	
Total testosterone (ng/dl)		41,63	
FSH(mUI/ml)		3,51	
Estradiol (ng/dl)		22	
LH(mUI/ml)		2,82	

TSH: thyroid- stimulating hormone; CK: creatine kinase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; FSH: Follicle stimulating hormone; Free T4: Free thyroxine; HDL: High density lipoprotein; LDL: low density lipoprotein; TG: triglycerides; beta-HCG: human chorionic gonadotropin; 25(OH)D: calcidiol

DISCUSSION

The term transgender refers to individuals whose gender identity does not match their sex assigned at birth. It might be subdivided into transgender male, characterized by a female anatomy but with a male gender identity, and transgender female, that shows a male anatomy but with a female gender identity. Gender identity is defined as one's own sense of recognizing themselves as a man, a woman or of an undetermined gender in relation to one's role in society, and is independent of biological sex. Transgender individuals present persistent discomfort, distress, and inadequacy in relation to their own gender, with consequent losses in social and occupational functions as well as in other areas (1,4).

Studies show that 0,5% of the adult population, or 25 million people in the world, are transgender. However, this number might be underestimated because the prevalence is directly related to the definition used to classify the transgender (5,6,7).

Lack of knowledge about the subject, either by the population as well as by health professionals, has made these individuals victims of prejudice and transphobia that comes from other members of society as well as the lack of family support. A study conducted in New York with 55 transgenders showed that 45% of them had suicidal ideas in some moment of their lives and 26% had already tried suicide. Considering these high rates, investigations of this subject are of extreme importance and they have been amplified with the attempt to better understand this topic (8).

Innumerous factors are analyzed to try to explain the physiopathology involved in the gender identity formation, such as disorders of sexual differentiation, genetic heritage, androgynous exposure as in congenital adrenal hyperplasia, neuroanatomical alterations, among others (2,9,10).

Many studies have reported cerebral differences between transgender individuals and control groups. Some of those have pointed to the existence of sexually dimorphic structures that are different not according to biological sex but according to gender identity. The bed nucleus of the stria terminalis (BSTc) well-known greater in men than in women showed a female figure in a group of female transgenders. However, the influence of these factors on gender identity formation still uncertain, indicating the need for more studies addressing this subject (8).

The transgender approach must always be taken in a multidisciplinary manner, engaging primary health professionals as first aid, mental health professionals to diagnose dysphoria or gender incongruence, endocrinologists for hormonal management, among others (4).

Hormonal replacement therapy in the transgender approach translates into ways to alleviate individual suffering and to help psychiatric disturbance treatment (3).

Before starting with replacement therapy, some important questions must be done. The doctor should discuss possibilities and limitations of hormonal treatment and sex reassignment surgery to avoid unrealistic expectations that might be created by the patient. Benefits and risks of treatment should also be discussed, such as the possibilities of loss of reproductive potential (1,3,11).

Hormonal replacement therapy has the purpose to reduce secondary biological sexual characteristics of patients by reducing endogenous hormones. Concomitantly, the objective is to assign hormonal replacement to the correspondent reassigned gender (3).

Male hormone replacement therapy is traditionally prescribed as intramuscular or transdermal injections. The primarily intramuscular forms of testosterone esters are cypionate, enanthate, and undecanoate. The recommended dosage for enanthate and cypionate is of 100 to 200 mg every 2 weeks or 50% of this dosage weekly. Testosterone undecanoate could be administered at a dosage of 1,000 mg every 12 weeks via intramuscular injection. Transdermal testosterone is available in a gel at 1%(2.5-10g/day) and patches (2.5-7.5 mg/day) (3).

Spratt et al. in his study involving 63 male transgender patients, pointed to the possibility of a subcutaneous route as an effective alternative to testosterone administration. In this study, weekly subcutaneous injections of 75-80 mg of testosterone cypionate showed good efficiency, reaching desired levels of testosterone as well as a satisfactory safety profile, avoiding the inconvenience of intramuscular injections (12).

The effects of hormonal replacement with testosterone, such as an increase in muscle mass and reduction of adipose tissue, should occur between 1 to 12 months of administration. Other side effects that should be expected include an increased growth of facial and body hair, acne, increased skin oiliness, androgenic alopecia, deepening of the voice and enhanced libido. Specifically, in transgender male patients, it can be found clitoral enlargement, decreased fertility and cessation of menses. It is important to note the possible deleterious effects of hormonal therapy as an increased chance of breast and uterus cancer (controversial), erythrocytosis, hypertension, dyslipidemia and hepatocellular lesion (3).

In order to control the possible deleterious effects, clinical and laboratory follow-up exams should be kept at every three months during the patient's first year of treatment, and at every six months or every year for the following years. Clinical exams should emphasize blood pressure and weight measurements, while laboratory exams should preconize hemogram, hepatic function, and transaminases, fasting plasma glucose and glycated hemoglobin (presence of diabetes and/or with risk factors). Considering that deleterious effects are dose-dependent, serum testosterone should always be required, and it should be maintained within normal reference ranges for men, between 350-750 ng/dl. Serum testosterone should be always measured in the mean interval between dosage administration in the case of enanthate and cypionate, and right before administration of following dose in the case of undecaonate. Estradiol levels must be measured during the first semester of follow-up or until a maximum of 6 moths of menses cessation, and its values should be maintained below 50 pg/dl (3).

The presence of risk factors, such as osteopenia or suspension of hormone therapy after gonadectomy in some transgender individuals, determine the necessity of bone densitometry that should be done from 60 years of age in the case of no other indications. If mastectomy was not performed and if there still uterine cervical tissue, a routine follow-up with mammography and oncotic colpocytology is recommended (3).

Chronic administration of testosterone seems to have a potential to increase the risks of ovarian cancer, secondary to the increase of androgen receptors in the ovarian tissue. (13). It is also important to consider hysterectomy with oophorectomy to reduce the risks of uterine and ovarian cancer and patient's discomfort during a gynecological exam. Nevertheless, it should be taken into account the risks and benefits associated with this procedure as well as patient's will (3).

Sex reassignment surgery is, to many transgender, an important phase of medical approach. In Brazil, according to the Federal Council of Medicine, patients are eligible for surgery only if they meet the following criteria: minimal age of 21 years, continuous and responsible use of hormonal therapy for at least 2 years; real life experience according to their gender identity for at least 1 year; continuous psychotherapy follow-up and patient's comprehension of all the practical issues that are related to surgery, such as cost, complications, rehabilitation and others (3).

CONCLUSION

Transsexuality is a complex topic that deserves significant attention by health professionals. It should always be approached by a multidisciplinary team capable of providing services such as psychotherapy, safe hormonal therapy based on scientific evidence and sex reassignment surgery according to patient's desire. Patients should always be followed and monitored, especially concerning possible adverse effects of hormonal therapy. Finally, there still need for more studies in this area to optimize our knowledge about this subject.

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