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JIM Journal of Interdisciplinary Medicine

Aims and scope

The Journal of Interdisciplinary Medicine aims to publish top quality papers related to any fields of medicine that present an interdisciplinary dimension.

The journal will mainly focus on recent advances in the field of diagnosis and treatment of the most common situations encountered in the clinical or research practice. Interdisciplinary approaches will be extremely welcomed, presenting new advances in the approach of different pathologies from the perspective of various clinical fields.

The Journal of Interdisciplinary Medicine will publish high-quality basic and clinical research related to interdisciplinary medical fields, in a common approach that will integrate the clinical studies with the pre-clinical work dedicated to the discovery of new mechanisms involved in the development and progression of a large spectrum of diseases.

The journal will try to provide the entire medical community with the perspective of the regional specifics of Central and Eastern European countries. The journal will primarily focus on publishing original research papers, but also other types of materials (such as review articles, case reports, state-of-the-art papers, comments to editor, etc) will be extremely welcomed.

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EDITORIAL

Medical Research During the COVID-19 Pandemic – Two Faces of the Same Coin

Diana Opincariu

"George Emil Palade" University of Medicine, Pharmacy, Science and Technology, Târgu Mureș, Romania

CORRESPONDENCE

Diana Opincariu
Str. Gheorghe Marinescu nr. 50
540136 Târgu Mureș, Romania
Tel: +40 372 653 100
E-mail: diana.opincariu@yahoo.ro

THE RISE OF A GLOBAL HEALTHCARE PROBLEM

The continuous growth of infections related to the novel coronavirus has affected the healthcare system and public health across the world. The World Health Organization (WHO) has declared COVID-19 outbreak a pandemic on March 11, 2020, when there were more than 20,000 patients with confirmed infections across Europe and the death toll has reached an estimated number of 1,000 people.[1] This is the first pandemic caused by a coronavirus, and the number of infected subjects, associated mortality rates, and the number of affected countries are expected to rise rapidly.[2] Therefore, several countries have started to implement national emergency measures to limit and mitigate the spread of infection. At this time, it is of utmost importance to provide sufficient resources to maintain the proper functioning of healthcare systems across the world.

The associated restrictions and measures are to be established at national levels, according to the resources and capabilities of each country. However, WHO strongly recommends the implementation of self-isolation measures, quarantines, and social distancing as soon as possible in order to flatten the curve of infection. The preventive and restrictive actions taken by governments may delay the spread of the virus, thus offering healthcare systems time to allocate the needed logistics for a smooth assimilation of the COVID-19 impact.[3]

As this unparalleled public health crisis is on the rise, it will distress not only the infected subjects and healthcare systems, but it will also take its toll on all societal sectors and individuals, including the economy, research, and industry. Therefore, there is an acute need for urgent research on all aspects of COVID-19 contagion, from genome sequencing and molecular studies, to observational ones that can better characterize the clinical characteristics of this novel disease, with its related complications, morbidity, and mortality. The relatively scarce information available on this pandemic includes the therapeutic measures as well. Currently, there are no proven effective and safe antiviral treatments, and hospitals across the globe are practicing emergency care and empirical treatments for the critically ill, as well as off-label medications that have been used for other

infectious diseases such as hydroxychloroquine or antivirals established for treating the influenza virus and HIV.[4]

CLINICAL RESEARCH DURING THE COVID-19 PUBLIC HEALTH EMERGENCY

In medical research during the COVID-19 era, there are two sides of the same coin, which should be preferably conducted in tandem. One side consists in continuing the pre-pandemic clinical trials using the main principles of a qualitative research, with a minimum delay in releasing safe and effective medications on the market. The other side of the coin consists in developing new research that addresses the crisis. Much of the resources allocated for medical research has been shifted towards COVID-19, with a focus on trials that have a large impact over a short amount of time. There is an immense pressure on the scientific community to conduct rapid, effective studies on COVID-19, and especially on treatment methods.[5] Such conduct may lead to decreased rigors in regards to research methodology, data generation, and interpretation, which may have deleterious effects on a global scale. The rapid conduction of clinical trials for effective treatments and vaccine against COVID-19 may lead to over- or misinterpretation of results. These may disseminate fast via lay media channels, and ultimately become endorsed by governments.[6] This will not only lead to a false sense of efficacy, but also to a redistribution of resources, away from other, promising studies. Despite the urgent need for new research and evidence on treatments and vaccines for COVID-19, the quality of studies should not be overlooked, as there is a risk for disseminating inaccurate data that can give false leads and ineffective and unsafe practices.

CLINICAL STUDIES – WORKING AROUND THE PROBLEM

The novel coronavirus pandemic has triggered important disruptions on the development and implementation of new clinical trials. It seems that this interruption will be prolonged as long as there is community contagion risk and circulation restrictions. This is of particular importance in medical areas that depend on experimental trials and testing of new drugs, especially in cancer research, but also in cardiovascular medicine. The short-term modifications triggered by the pandemic are caused by the reallocation of human and financial resources to COVID-19-supporting hospitals, and also cessation of research activities in academic institutions and university hospitals. This will ultimately lead to long-term effects including delayed drug development and testing, thus negatively affecting patient outcomes.[7] Protocol deviations and impossibility to initiate new medication trials will not only affect future therapeutic managements, but will also come with detrimental financial implications. In addition, there may be a delay or lack in reporting adverse events in clinical trials for medical and pharmacological products, which could affect patient safety on the long term. There should also be a very robust and accurate report in case of infection or COVID-19-related deaths of study participants, as it can affect survival end-points in certain studies.[8]

GUIDANCE RECOMMENDATIONS FOR ONGOING CLINICAL TRIALS DURING THE COVID-19 PANDEMIC

The COVID-19 outbreak at a worldwide level comes with subsequent alterations of ongoing clinical trials. Several measures taken by the authorities for decreasing contagion and increasing healthcare efficacy will lead to study protocol deviations. Additional challenges may result from closure of sites, travel limitations, and interruptions in the supply chain of the tested medical product, but also the infection of study subjects and site investigators. Such protocol deviations should be documented and preferably not impact the future results of current trials. In order to ensure a minimum disruption in the integrity of clinical trials during the SARS-CoV2 pandemic, the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have both issued guidance documents for the management of ongoing studies of medical products. Both guideline documents have a common clear goal to assure patient safety with a minimum to null risk for infection, while complying with Good Clinical Practices.[9,10] If the safety of study participants and investigators is put at risk, the proposed measures can go to such lengths as to temporarily cease recruitment and prioritize critical activities for the already enrolled subjects. For experimental drug trials, due to the required social distancing and limitation of outdoor activities, one option could include shipments of study medications and products to patients' homes. However, this approach is feasible in case of study interventions that can be self-administered and do not require in-hospital settings and monitoring. Also, study products should be transported in accordance with the labelled storage conditions, with thorough records of storage, transportation, and destructions of the drug. Another proposed safety measure refers to patient monitoring and study visits, which should be reorganized by using remote electronic and telephone visit protocols. Some presched-

uled visits are crucial in assessing patient safety, or require imaging or laboratory analysis. If the patient is exposed to unacceptable risk, the recommended option is to either discontinue study participation, or to refer the patient to an alternative lower risk study site. Anyhow, the recommended strategy is to implement alternative processes for study procedures, visits, and supplying the study products in a manner as consistent as possible to the original protocol, in order to ensure a minimum disruption in finalizing the research, while eliminating hazards and COVID-19 exposure.[8–10]

MAJOR TRIALS FOR REPURPOSING ESTABLISHED THERAPEUTIC AGENTS TOWARDS CORONAVIRUS

There are a multitude of interventional clinical studies that have been initiated in an attempt to provide safe and effective therapeutic options for COVID-19 infection. Two large multicenter studies have been approved for conducting a comparative analysis between several treatments used for other conditions, which have also been used off-label in COVID-19 patients. Both trials aim to generate robust information regarding the most effective therapeutic strategies for COVID-19. The Solidarity international trial provides a flexible, simplified research platform for testing 4 existing anti-inflammatory and antiviral agents (remdesivir vs. lopinavir-ritonavir, lopinavir-ritonavir combined with interferon-beta vs. hydroxychloroquine) in comparison to local standards of care. The simplified study protocol and flexibility will enable study sites to provide the complete required study data, even in overloaded hospitals that are designated to treat coronavirus patients.[11] The RECOVERY trial (Randomised Evaluation of COVID-19 Therapy) will comparatively study the effect of 4 potential treatments for COVID-19 infection (lopinavir-ritonavir vs. low-dose dexamethasone vs. hydroxychloroquine vs. tocilizumab). As data from the trial will emerge, the intermediate results will be made public, and any effective treatment will be made available for all patients. Study end-points for RECOVERY include in-hospital death, discharge, and the need for ventilation. The innovative characteristic of this study will be that, if there is a new promising therapeutic agent, it will be included in the study, in addition to the already included medications.[12]

CONCLUSIONS

The rapid spread of COVID-19 across the world has impacted all aspects of life. The need for effective and safe therapies is acute and can only be established by conducting flexible, simple randomized clinical trials. However, the quality and methodology of medical research is not to be dismissed. Trial misconducts can have a huge impact on the evolution of this pandemic, on a global scale, and they may also lead to improper allocation of financial and human resources. In addition to shifting the research interest and funds towards COVID-19, the ongoing clinical trials should not be neglected. Study procedures and visits should limit the risk of infection for the study participants. If the safety of the subject is put at risk, temporary or permanent cessation of the study should be taken into account. The COVID-19 pandemic is currently dominating all aspects of medical research and healthcare resources. The longer its spread across time, the more obstacles will appear during the aftermath. This will completely change the world of clinical research and will impact future results of studies and trials, in all medical areas.

CONFLICT OF INTEREST

Nothing to declare.

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ORIGINAL RESEARCH

DIABETOLOGY // REPRODUCTIVE HEALTH

Reproductive Health and Metabolic Parameters in Women with Type 2 Diabetes

Corina Roxana Onea[1], Beáta Máté[1,2], Simona Cernea[3,4]

[1] Emergency County Clinical Hospital, Târgu Mureş, Romania
[2] Doctoral School of I.O.S.U.D., "George Emil Palade" University of Medicine, Pharmacy, Science, and Technology, Târgu Mureş, Romania
[3] Department M4/Internal Medicine IV, "George Emil Palade" University of Medicine, Pharmacy, Science, and Technology, Târgu Mureş, Romania
[4] Diabetes, Nutrition and Metabolic Diseases Outpatient Unit, Emergency County Clinical Hospital, Târgu Mureş, Romania

CORRESPONDENCE

Simona Cernea
Str. Gheorghe Marinescu nr. 38
540139 Târgu Mureș, Romania
Tel: +40 265 215 551
E-mail: simonacernea@yahoo.com; simona.cernea@umfst.ro

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Corina Onea • Str. Gheorghe Marinescu nr. 7B, 540140 Târgu Mureș, Romania. Tel:+40 727 755 581, E-mail: corinaroxanarata@yahoo.ro

Beáta Máté • Str. Gheorghe Marinescu nr. 50, 540136 Târgu Mureș, Romania. Tel: +40 743 045 282, E-mail: juhos_beata@yahoo.com

ABSTRACT

Aim: This study evaluated the correlations between metabolic parameters and reproductive health data in women with type 2 diabetes mellitus (T2DM). **Material and methods:** In this observational retrospective study, data from the medical records of 324 adult women with T2DM attending their regular diabetes check-ups were collected and analyzed (i.e., anthropometric parameters at first outpatient visit and yearly thereafter, first recorded HbA1c and all HbA1c for the entire follow-up duration, as well as obstetrical/gynecological information). **Results:** Age at the diagnosis of T2DM correlated positively with age at menarche (r = 0.21, [95% CI: 0.09, 0.31], p = 0.0002) and age at menopause (r = 0.18 [95% CI: 0.07, 0.29], p <0.01). Age at menarche correlated negatively with mean weight (r = –0.21 [95% CI: –0.31, –0.10], p: 0.0002) and mean BMI (–0.22 [–0.32, –0.11], p <0.0001) over the follow-up time. Patients with shorter time difference between age at menarche and age at onset of T2DM (≤45 years) had higher mean weight (83.8 ± 14.5 kg vs. 78.4 ± 16.0 kg, p = 0.0001), BMI (33.2 ± 5.6 kg/m^2 vs. 31.8 ± 5.7 kg/m^2, p <0.05), and HbA1c over time (6.9 ± 0.8% vs. 6.6 ± 0.9%, p <0.0001). Women with T2DM with earlier menarche (<12 years old), with irregular menses during their reproductive life, and ≥3 pregnancies had higher overall BMI, but mean HbA1c were not significantly different. However, women diagnosed with T2DM before menopause had a higher mean HbA1c over time (7.1 ± 0.8% vs. 6.7 ± 0.9%, p <0.01). **Conclusion:** The BMI correlated with several indicators of reproductive health (earlier menarche, irregular menses, and higher number of pregnancies), while earlier onset of T2DM influenced metabolic control in women with T2DM.

Keywords: type 2 diabetic women, menarche, menopause, puberty

INTRODUCTION

Over the past decades, the worldwide prevalence of diabetes mellitus has increased, and it is estimated to affect 578 million adults by 2030 and 700 million by 2045.[1] Moreover, the increasing prevalence of type 2 diabetes mellitus (T2DM) has emerged in parallel with a secular decrease in the average age at menarche.[2,3] Thereby, the association between puberty onset and T2DM could relate not only to changes in lifestyle and environment, but also to the associated

biological processes.[2] On the other hand, sexual dysfunction occurs in a large proportion of diabetic women, which poses further burden on their reproductive lifespan.[4] Therefore, it is important to acknowledge the correlations between reproductive health and T2DM.

Some data show that women with a younger age at menarche have a greater risk to develop T2DM later in life, but not all studies agree.[5,6] Part of the explanation may be related to body adiposity, translated by a higher adult body mass index (BMI).[2] However, the association between early onset of puberty and adult BMI remains debated because girls with a younger age at menarche already have a higher BMI at that time.[7] Results from the EPIC-Norfolk cohort study indicate that the risk of diabetes is 10% lower with every year of delay in the age at menarche.[6] The study has also shown that age-adjusted adult BMI is lower by 0.43 kg/m^2 per year, while the waist circumference is lower by 0.74 cm per year for each year of delay in the onset of menarche.[8]

On the other hand, some studies have demonstrated that women with T2DM have an earlier onset of menopause, and metabolic disorders, such as T2DM, accelerate reproductive ageing with premature ovarian failure.[9,10] A study from 11 Latin American countries has shown that the presence of T2DM triples the risk of early menopause in women under the age of 45.[11]

There is, however, relatively scarce data regarding the correlations between long-term glycemic control and age at menarche/menopause, as well as other aspects of reproductive health in women with T2DM.

We therefore aimed to evaluate the correlations between metabolic data and age at menarche/menopause and other indicators of reproductive health in women with T2DM.

MATERIAL AND METHODS

This was an observational retrospective study, in which data from the medical records of adult women with T2DM, attending the Diabetes Outpatient Unit of the Emergency Clinical County Hospital of Târgu Mureș, were collected. The study has been approved by the Ethics Committee of the Emergency Clinical County Hospital of Târgu Mureș. The patients attended the outpatient clinic for regular check-ups between February and August 2019. They have been diagnosed with diabetes mellitus according to the diagnostic criteria of the American Diabetes Association.[12] The following data were recorded: date of birth, age at diagnosis of diabetes, duration of diabetes, weight and height at first outpatient visit, weight (yearly thereafter, for the entire duration of follow-up), first recorded HbA1c and every HbA1c thereafter (for the entire duration of follow-up). The BMI was calculated at the first visit and once a year thereafter, for the entire duration of follow-up, based on the formula: BMI = weight/height^2 (kg/m^2). Mean weight, BMI, and HbA1c for the follow-up duration were calculated.

In addition, the following obstetrical/gynecological (Ob/Gyn) information was collected from the medical charts: age at menarche, number of pregnancies, number of births, age at menopause onset, regularity of menses, and age at which hysterectomy was performed (if applicable). For women who have reached menopause, the reproductive lifespan was calculated as the difference between age at menopause and age at menarche.

Statistical analysis was performed using descriptive and inferential statistics. Continuous variables with normal distribution were expressed as mean ± SD and those with non-gaussian distribution as median (min–max), while categorical variables were presented as frequency (%). Means and medians of different groups were compared using Student's t-test or the Mann-Whitney test, as well as ANOVA or the Kruskal-Wallis test, respectively. Fisher's exact test was employed to analyze categorical variables. The correlations between variables of interest were tested using the Pearson's or Spearman's tests, respectively, and data is presented as r (95% confidence interval [CI]). All tests were two-tailed, and statistical significance was set at $p < 0.05$.

RESULTS

Data from 324 female patients with T2DM were collected and analyzed, and are presented in Table 1.

The correlations between metabolic and Ob/Gyn data were analyzed. Age at diagnosis of diabetes correlated positively with age at menarche (r = 0.21 [95% CI: 0.09, 0.31], p = 0.0002, Figure 1) and age at menopause (r = 0.18 [95% CI: 0.07, 0.29], p <0.01), but not with the number of pregnancies (r = 0.09 [95% CI: –0.03, 0.20], p = 0.12), number of births (r = 0.05 [95% CI: –0.06, 0.16], p = 0.36), or having regular menses (r = –0.09 [95% CI: –0.20, 0.02], p = 0.11). On the other hand, age at diagnosis of diabetes correlated negatively with mean BMI over time (r = –0.24 [95% CI: –0.35, –0.14], p <0.0001) and mean HbA1c over time (r = –0.26 [95% CI: –0.36, –0.15], p <0.0001).

Age at menarche correlated negatively with mean weight over time (r = –0.21 [95% CI: –0.31, –0.10], p = 0.0002), first recorded weight (r = –0.21 [95% CI: –0.31, –0.10], p = 0.0002), mean BMI over time (r = –0.22 [95% CI: –0.32, –0.11], p <0.0001), and first recorded BMI

TABLE 1. Ob/Gyn and metabolic data of the study population. Data are presented as mean ± SD or median (min–max); *for women who have reached menopause

	Women with T2DM n = 324
Age (years)	65.3 ± 8.8
Age at menarche (years)	14.0 (9.0–20.0)
Number of pregnancies	2.0 (0–14.0)
Number of births	2.0 (0–8.0)
Regular menses (n/%)	284/87.6
Age at menopause (years)	49.0 (26.0–59.0)
Reproductive lifespan* (years)	35.0 (13.0–44.0)
Menopause due to hysterectomy (n/%)	38/11.7
Age at hysterectomy (years)	43.0 ± 7.1
Age at diagnosis of diabetes (years)	59.0 (24.0–82.0)
Duration of diabetes (years)	7.0 (0–31.0)
First recorded weight (kg)	79.7 (49.0–134.0)
Overall weight (kg)	78.7 (49.8–136.7)
First recorded BMI (kg/m2)	32.3 (20.1–52.7)
Overall BMI (kg/m2)	31.9 (20.2–51.4)
First recorded HbA1c (%)	6.6 (3.9–14.0)
Overall HbA1c (%)	6.7 (5.2–13.12)

(r = –0.22 [95% CI: –0.33, –0.11], p <0.0001, Figure 2). However, it did not correlate with HbA1c at first visit (r = –0.02 [95% CI: –0.13, 0.09], p = 0.69) or overall HbA1c (r = –0.04 [95% CI: –0.15, 0.07], p = 0.47).

We have further analyzed the correlations between age at menarche and T2DM. The study group was therefore divided into two subgroups based on the time difference between age at menarche and age of T2DM onset (≤45 years and >45 years, 45 years being the median value). Patients with a shorter time difference (≤45 years) had higher weight (83.8 ± 14.5 kg vs. 78.4 ± 16.0 kg, p = 0.0001), higher BMI (33.2 ± 5.6 kg/m^2 vs. 31.8 ± 5.7 kg/m^2, p <0.05), and higher mean HbA1c over time (6.9 ± 0.8% vs. 6.6 ± 0.9%, p <0.0001).

Finally, we have divided the study group into three subgroups based on age at the onset of menarche: early- (<12 years old; n = 23), normal- (12–16 years old; n = 263), and late-onset menarche (≥16 years old; n = 38). The earlier the menarche, the higher was the overall weight (84.8 ± 2 kg vs. 81.8 ± 15.3 kg vs. 75.3 ± 11.1 kg, p <0.05) and BMI (Figure 3), but the mean overall HbA1c was not significantly different between the groups (6.5 ± 0.5% vs. 6.8 ± 0.8% vs. 6.8 ± 1.4%, p = 0.23).

Women with T2DM who have self-reported to have had irregular menses during their reproductive lifespan had higher overall BMI (34.5 ± 6.0 kg/m^2 vs. 32.2 ± 5.6 kg/m^2, p <0.05) compared to women with regular menses, but there was no difference between their metabolic control (HbA1c: 6.7 ± 0.5% vs. 6.8 ± 0.9%, p = 0.87).

Women with T2DM with higher than median number of pregnancies (≥3) had higher overall BMI (33.1 ± 5.4 kg/m^2 vs. 32.1 ± 5.9 kg/m^2, p <0.05), but no different mean HbA1c (6.8 ± 0.7% vs. 6.8 ± 1.0%, p = 0.44) compared with women with <3 pregnancies. The same trend was seen for

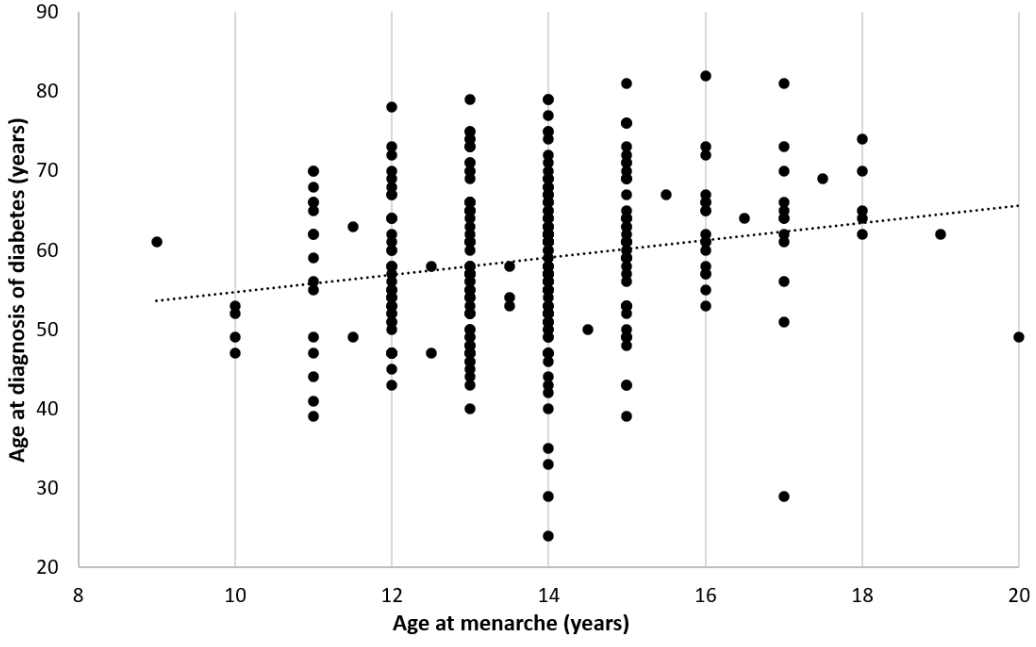

FIGURE 1. Correlations between age at menarche and age at diagnosis of T2DM (data are r [95% CI])

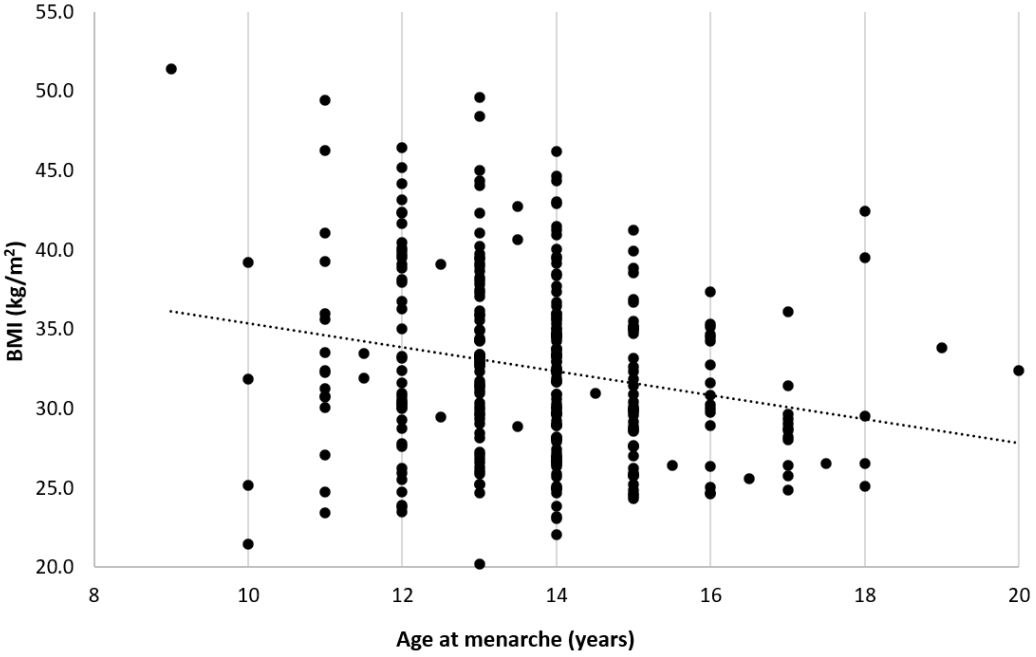

FIGURE 2. Correlations between age at menarche and mean overall BMI (data are r [95% CI])

the number of births (≥3 versus < 3 births), but it did not reach statistical significance (mean BMI: 33.2 ± 5.4 kg/m² vs. 32.3 ± 5.8 kg/m², p = 0.08; mean HbA1c: 6.8 ± 0.7% vs. 6.7 ± 0.9%, p = 0.09).

Age at menopause did not correlate with the first recorded BMI (r = 0.01 [95% CI: –0.10, 0.12], p = 0.85), mean overall BMI (r = 0.01 [95% CI: –0.11, 0.12], p: 0.90), first recorded weight (r = 0.01 [95% CI: –0.10, 0.13], p = 0.82), or overall weight (r = 0.002 [95% CI: –0.11, 0.12], p = 0.97). The same was true for mean overall HbA1c (r = 0.06 [95% CI: –0.06, 0.17], p = 0.30), or HbA1c at first visit (r = 0.08 [95% CI: –0.04, 0.19], p = 0.18).

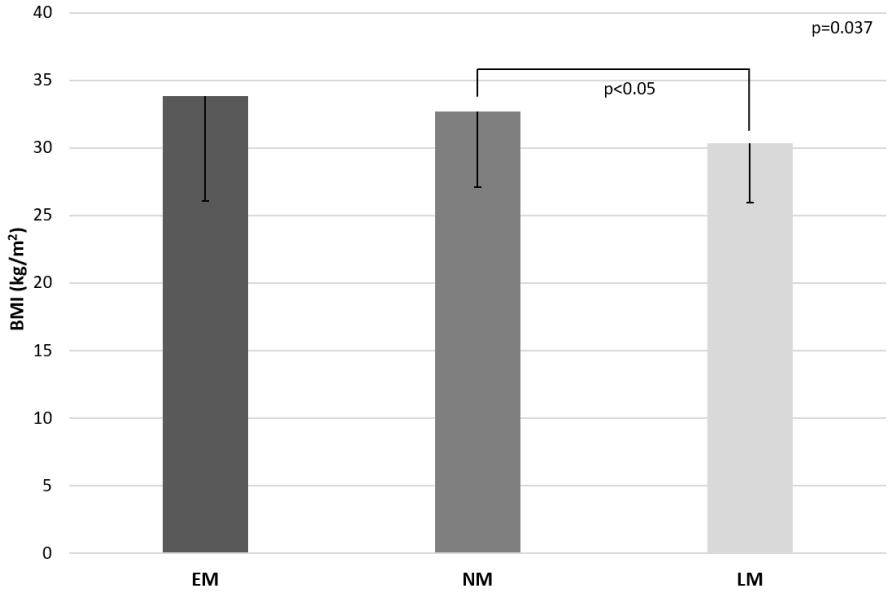

FIGURE 3. Overall mean BMI in the three subgroups divided based on age at the onset of menarche (EM – early menarche, <12 years old; NM – normal menarche, 12–16 years old; LM – late menarche, >16 years old)

There was no difference in BMI between the group that developed T2DM before/at the same time with menopause and the group that was diagnosed with T2DM after the menopause (32.9 ± 6.7 kg/m2 vs. 32.5 ± 5.6 kg/m^2, p = 0.80), and the same was true for weight (84.1 ± 16.8 kg vs. 80.9 ± 15.2 kg, p = 0.26). However, women who were diagnosed with T2DM before the onset of menopause had a higher mean HbA1c over time (7.1 ± 0.8% vs. 6.7 ± 0.9%, p <0.01).

DISCUSSIONS

The first finding of this study was the positive association between age at menarche and age at the onset of T2DM, which was in agreement with reported data showing that pubertal timing in younger ages is associated with a higher risk of T2DM.[2] In our study, women with early menarche (<12 years old) had higher overall weight and BMI, which may explain the onset of T2DM later in life. According to the (EPIC)-InterAct case-cohort study, women with an early menarche (8–11 years old) had a 70% higher risk of T2DM compared to those with age at menarche between 12–16 years.[2] Apart from body adiposity, there are other suggested explanations for the link between puberty timing and diabetes. One of them is that low serum sex hormone-binding globulin (SHBG) levels associated with high plasma sex hormones (estradiol and testosterone) induced by earlier menarche could influence the glycemic status and correlate with higher risks of diabetes.[13,14]

T2DM patients with a shorter duration between age at menarche and age at the onset of diabetes had higher mean HbA1c, but age at the onset of puberty was not correlated with later glycemic control. Contrary to our findings, a large study from China has indicated that early age at menarche was associated with worse metabolic control (HbA1c >7%).[15] However, the thresholds for menarche age used to separate the subgroups in that study were different (<15 years old, 15–18 years old, and >18 years old, respectively).[15] Moreover, the mean HbA1c in these subgroups were similar (p = 0.37), which is in concordance with our study.

Another finding of this study is that there was a weak positive correlation between age at the diagnosis of T2DM and age at menopause. A South Indian study found a significant difference between age at menopause in women with and without diabetes (p <0.01), and that in women with diabetes, the average age at menopause was 4 years younger than in the general population.[10] The process of premature ovarian failure and progressive reproductive ageing could be partially explained by the presence of diabetes.[10] However, the literature is not completely concordant, as an earlier study did not indicate a significant difference between age at menopause in women with or without T2DM.[16] There is limited data regarding metabolic control and age at menopause in women with T2DM. A study by Shen *et al*. indicated that Chinese women with T2DM with early and late menopause had worse glycemic control.[15] We found no direct correlation between age at the onset of menopause and overall glycemic control, but women who were diagnosed with diabetes before menopause had higher overall HbA1c, although there were no differences between BMIs. This may imply that poorer glycemic control was not mediated by body adiposity, and other factors may have a role.

Additionally, the frequency of irregular menses and oligomenorrhea is much higher in both type 1 and type 2 diabetic patients compared to healthy subjects.[17] The prevalence of irregular menstrual cycles varies from 5% to 35.6% in different studies depending on age, occupation, and residence.[18] In our study, this prevalence was 12.4%. One small study in Korean women reported that the frequency of oligomenorrhea was about two-fold higher in women with T2DM vs. controls (16.1% vs. 8.5%).[19] Similar results were shown in a North Indian study reporting that the prevalence of oligomenorrhea was higher in obese vs. non-obese women with T2DM vs. healthy controls (16.4% vs. 8.8% vs. 0%; p = 0.014).[20] It seems that there is a bidirectional relationship between T2DM and menstrual cycle irregularities, as several studies have shown that women with irregular menstrual cycles have a significantly higher risk for developing T2DM.[21] In a more recent report from the Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study, menstrual dysfunction was more frequent in girls with recently diagnosed T2DM (21%) and was associated with alterations in sex steroids and SHBG levels, but not in β-cell function or insulin sensitivity.[22] This apparently did not improve significantly after two years of antihyperglycemic therapy, but it was slightly lower at 12 and 24 months (15% and 11%, respectively).[22] Similarly, our data indicate that women with self-reported irregular menses during their reproductive life had higher BMI, but not a significantly different metabolic control. A cross-sectional study in 220 young women indicated a significant association between overall and central obesity with menstrual cycle irregularity, while an earlier report of the Nurses' Health Study II showed that women with long/highly irregular menses present a higher risk of T2DM not entirely explained by obesity.[23,24] Thus, the complex association between obesity, T2DM, and menstrual cycle irregularities needs further research.

In our study, a shorter duration between menarche and onset of T2DM (≤45 years) was associated with worse outcomes in terms of glycemic control over time compared with women with longer duration, and also with higher body adiposity, but this could be rather related with earlier onset of T2DM.

CONCLUSIONS

This study has shown that age at the diagnosis of T2DM correlated positively with age at menarche and age at menopause. The BMI correlated with several indicators of reproductive health (earlier menarche, irregular menses, and higher number of pregnancies), while earlier onset of T2DM influenced metabolic control in women with T2DM.

CONFLICT OF INTEREST

Nothing to declare.

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ORIGINAL RESEARCH

DERMATOLOGY // EPIDEMIOLOGY

The Utility of a Questionnaire Proposal as an Analytic Diagnostic Tool in Healthcare Providers Occupational Hand Eczema

Anca E. Chiriac[1], Tatiana Taranu[2], Anca Chiriac[3,4,5], Simona Roxana Georgescu[6], Liliana Foia[7], Cristian Podoleanu[8], Simona Stolnicu[9], Doina Azoicai[10]

[1] "Grigore T. Popa" University of Medicine and Pharmacy, Iași, Romania
[2] Department of Dermatology, "Grigore T. Popa" University of Medicine and Pharmacy, Iași, Romania
[3] Department of Dermatology, Nicolina Medical Center, Iași, Romania
[4] Apollonia University, Iași, Romania
[5] "Petru Poni" Institute of Macromolecular Chemistry, Romanian Academy, Iași, Romania
[6] Department of Dermatology, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
[7] Department of Biochemistry, "Grigore T. Popa" University of Medicine and Pharmacy, Iași, Romania
[8] Department of Internal Medicine IV, "George Emil Palade" University of Medicine, Pharmacy, Science and Technology, Târgu Mureș, Romania
[9] Department of Pathology, "George Emil Palade" University of Medicine, Pharmacy, Science and Technology, Târgu Mureș, Romania
[10] Department of Epidemiology, "Grigore T. Popa" University of Medicine and Pharmacy, Iași, Romania

CORRESPONDENCE

Simona Stolnicu
Str. Gheorghe Marinescu nr. 38
540139 Târgu Mureș, Romania
Tel: +40 265 215 551
E-mail: stolnicu@gmx.net

ARTICLE HISTORY

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Anca E. Chiriac • Str. Universității nr. 16, 700115 Iași, Romania. Tel: +40 232 301 600

Tatiana Taranu • Str. Universității nr. 16, 700115 Iași, Romania. Tel: +40 232 301 600

Anca Chiriac • Str. Hatman Șendrea nr. 2, 700613 Iași, Romania. Tel: +40 332 808 703

Simona Roxana Georgescu • Blv. Eroii Sanitari nr. 8, 050474 București, Romania. Tel: +40 21 318 0719

Liliana Foia • Str. Universității nr. 16, 700115 Iași, Romania. Tel: +40 232 301 600

Cristian Podoleanu • Str. Gheorghe Marinescu nr. 38, 540139 Târgu Mureș, Romania. Tel: +40 265 215 551

Doina Azoicai • Str. Universității nr. 16, 700115 Iași, Romania. Tel: +40 232 301 600

ABSTRACT

The aim of this study was to estimate the prevalence of self-reported work-related and occupational hand eczema, as well as associated risk factors in hospitals and out-patient clinics in Romania. A standardized questionnaire was addressed to health professionals from different medical fields. Out of 245 healthcare providers who completed the survey, 235 were women (95.9%), and 243 were working more than 8 hours/day in hospitals (99.18%). Hand eczema was self-reported and documented in almost one third of the nurses (33.49%), the most frequently involved trigger factor being powdered latex gloves. A total of 207 (84.48%) individuals denied any present or past allergic diseases. Only one nurse declared that severe hand eczema was the cause of losing her job at the hospital. Exposure assessment is essential for the diagnosis of work-related or occupational skin diseases.

Keywords: occupational hand eczema, healthcare providers, questionnaire

INTRODUCTION

Occupational skin diseases should be a priority public health issue since they represent up to 30% of occupational diseases.

The recognition of occupational skin diseases is important for improving prevention and patient management, due to their significant economic and social impact on each individual and the society. Occupational hand eczema among

health care providers has a great impact on their quality of life and professional activity.

The aim of this study was to gather information on hand eczema and its risk factors from persons working in hospitals and outpatient clinics in different cities in Romania.

MATERIAL AND METHOD

The study was based on a self-reported questionnaire addressed to employees of medical units, focusing on hand eczema, trigger factors, associated diseases, and protective measures.

The questionnaire was anonymous, simple, short (three pages), easy to understand and to fill in, with yes or no answers to specific questions, and it concentrated on clinical aspects related to direct work exposure.

Details about work aggravating factors, such as contact with chemical agents (detergents, disinfectants, soap, liquid soap, shampoo and other personal hygiene products, or skin cleanser), use of latex or other types of gloves (plastic, cotton, natural, or synthetic rubber), other suggestive exposures, and frequency of hand washing, were considered.

The medical history of the persons enrolled in the study was also recorded, especially the presence of an atopic and allergic background, as well as the presence of comorbidities, chronic treatments or other exposures such as UV radiation.

RESULTS

A total of 1,000 questionnaires were distributed to employees from all job groups and all departments in hospitals and ambulatory units from main cities in Romania. However, only 245 questionnaires were validated, yielding a positive response rate of 24.50%. This small percentage confirms the possible underestimation of the prevalence of occupational or work-related hand eczema among healthcare providers in the entire country. Possible explanations of the low participation to the study could be indifference to the subject, lack of understanding of all questions, fear of correct answers that can affect daily activity, unwillingness to recognize the existence of symptoms, and lack of compliance or knowledge.

The great majority (235 out of 245) of questionnaires confirmed that women are prevalent in this working sector, more specifically: 82 (33.46%) nurses and 161 (65.71%) medical assistants were women. It should be mentioned here that in Romania a nurse's activities include mainly cleaning and disinfecting, while the medical assistant corresponds to a nurse in Western countries. Physicians did not want to take part in the study; only one questionnaire was filled out by a surgeon. Moreover, domestic activities, such as washing the dishes by hand, could also influence the prevalence of hand eczema in women by increasing exposure to irritants at home.

TABLE 1. Analysis of responses incriminating gloves at work

Response	N	%
Yes	64	26.12
No	165	67.34
Denied	16	6.53
Total	245	

TABLE 2. Analysis of the types of gloves used at work

Glove type	N	%
Latex, powdered	204	83.3
Latex, no powder	41	16.7
Rubber	13	5.3
Unknown	7	2.9
Nitrile	2	0.8
Neoprene	1	0.4
Polyethylene	1	0.4
Vinyl	1	0.4
Response missing	9	3.7

The responders were separated into age groups, and statistics showed a higher frequency of hand eczema reported by healthcare providers older than 40 years compared to younger responders.

Atopic dermatitis was not reported by anyone enrolled in the study; 207 (84.48%) responders denied any type of allergy; rhinitis was reported by 12 (4.90%) responders, asthma by 10 (4.90%), urticaria by 10 (4.09%), oral type of allergy by 2 (0.82%), and unknown type of allergy by 10 (4.08%) responders. Moreover, 207 (83.80%) responders denied having any type of allergy among family members.

Regarding smoking, the results were astonishing and potentially implausible because only 27 (10.93%) responders admitted to smoking compared to 217 (87.84%) who denied and 3 (1.2%) who missed to answer.

The use of protective gloves was reported by 223 (91.02%) responders, and 67 (27.12%) responders incriminated protective gloves, especially powdered latex gloves, as the cause of skin lesions (Table 1 and 2). Contact with other agents was evaluated by answers to specific questions (Table 3).

Hand washing was quantified as rare (0–5 times/day), usual (6–10 times/day), frequent (11–20 times/day), or permanent (more than 20 times/day); it was significantly more frequent among positive responders (Table 4).

TABLE 3. Analysis of other incriminating agents

Agent	N	%
Detergents	7	2.86
Soap	6	2.45
Kallas	5	2.04
Talcum	5	2.04
Y	4	1.63
Bed sheets	1	0.41
Unknown chemical agents	1	0.41
Chloramine	1	0.41
Chlorhexidine	1	0.41
Unknown disinfectant	1	0.41
Response missing	220	89.79
Total	245	

KALLAS and Y are cleaning products labeled by responders, and talc is the white powder usually found in gloves.

TABLE 4. Analysis of hand washing frequency

No. of hand washes per day	N	%
>20 (permanently)	192	77.73
911–20 (frequently)	31	12.55
6–10 (usually)	10	4.04
0–5 (rarely)	3	1.21
As necessary	1	0.40
No washing	1	0.40
Response missing	9	3.64

TABLE 5. Analysis of the prevalence of wet hands

Prevalence of wet hands (min/day)	N	%
Permanently	1	0.40
Frequently (>120)	66	26.72
Often (30–120)	56	22.67
Rarely (<30)	105	42.51
Response missing	19	7.69

An important question was addressed to responders, trying to estimate the concept of "wet hands", defined by prolonged contact with water (minutes/day) without protective measures; responses were classified as frequent, rare, often, and permanent. The results, summarized in Table 5, confirm the importance of a wet environment in inducing occupational hand eczema.

DISCUSSION

To the best of our knowledge, no data has been published on the incidence of occupational hand eczema in healthcare providers in Eastern Europe.

The present study is based on the random distribution of anonymous questionnaires to 1,000 healthcare providers from hospitals and out-patient clinics spread to all corners of the country. The response rate (24.5%) is nevertheless low in contrast to other, similar studies (65% in a study performed in Denmark in 2007).[1]

Although compared to a clinical examination the validity of a questionnaire study is debatable, it allows an anonymous investigation on a larger scale, a non-homogenous study population, and the collection of variable additional data. The results of self-reported eczema studies have been validated in many studies.[2,3] Several Swedish analyses, based on self-reported occupational hand eczema, have concluded a sensitivity of 87% and a specificity of 79%.[3]

The present study confirms the frequency of occupational eczema in women, especially in nurses, in accordance with other reports in which 70–72% of occupational skin disorders have been diagnosed in female nurses.[4]

Although they are preventive measures, protective gloves, the use of disinfectants, and hand washing proved to be risk factors for occupational hand eczema.

Compared to other similar studies however, the present study indicates a higher positive rate of responders among women over 40 years of age, which is in contrast to other reports.[5]

CONCLUSION

In conclusion, hand eczema can be documented in almost one third of the nurses, and the most frequent factor involved in triggering hand eczema may be represented by powdered latex gloves.

CONFLICT OF INTEREST

Nothing to declare.

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CLINICAL UPDATE

CARDIOLOGY // UROLOGY

Renal Denervation – a Modern Option for Treating Resistant Hypertension

Ioana Rodean[1], Călin Chibelean[2]

[1] Clinic of Cardiology, "George Emil Palade" University of Medicine and Pharmacy, Science and Technology, Târgu Mureș, Romania
[2] Clinic of Urology, County Clinical Hospital, "George Emil Palade" University of Medicine and Pharmacy, Science and Technology, Târgu Mureș, Romania

CORRESPONDENCE

Ioana Rodean
Str. Gheorghe Marinescu nr. 38
540139 Târgu Mureș, Romania
Tel: +40 265 215 551
E-mail: ioana_patricia@yahoo.com

ARTICLE HISTORY

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ABSTRACT

Hypertension is one of the main cardiovascular risk factors, and it remains an important health problem, demonstrating an increasing incidence despite new treatment methods. Numerous risk factors that can lead to the development of difficult-to-treat or resistant hypertension have been described in the literature in recent years. In this type of hypertension, an important role is played by the sympathetic nervous system. Especially in these cases, with a sympathetic overactivation, renal denervation has proven its efficacy and safety in lowering blood pressure. In this brief clinical update, we present the results of the main studies regarding the efficacy and safety of the renal denervation technique used in the treatment of resistant hypertension.

Keywords: resistant hypertension, renal denervation, sympathetic nervous system

INTRODUCTION

Although there are various new therapeutic techniques, hypertension remains one of the major cardiovascular risk factors. Numerous antihypertensive therapeutic strategies, including pharmacological agents such as diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium-channel blockers, anti-renin drugs, antiadrenergic or new molecules such as firibastat or empaglifozin, are available on the market, but renal ablation/denervation remains one of the most important and successful therapeutic options for resistant cases of hypertension. However, due to its invasive nature, this therapeutic method is not routinely recommended.[1,2]

An important role in the etiology of hypertension is played by the genetic factor interconnected with environmental, behavioral, and social factors. Globally, more than 1 billion people are suffering from hypertension, which contributes to 218 million disability-adjusted life years. According to the World Health Organization, uncontrolled hypertension produces 9.4 million deaths per year.[1,3,4]

Resistant or difficult-to-control hypertension is defined as a constant high blood pressure (above 140/90 mmHg) which is uncontrolled despite the phar-

Călin Chibelean • Str. Gheorghe Marinescu nr. 1, 540103 Târgu Mureș, Romania. Tel: +40 265 215 133, E-mail: calinchibelean@yahoo.com

macological use of three antihypertensive agents, including a diuretic, for at least one month without any interruption. This state of resistance is caused by numerous metabolic factors such as obesity, diabetes mellitus, sleep apnea syndrome, alcohol intake, volume overload, thyroid disease, or even chronic kidney disease. It is estimated that up to 40% of patients with chronic kidney disease will develop uncontrolled hypertension. Also, these patients are at an increased risk of developing coronary or peripheral artery disease, stroke, or vascular dementia.[1,5–7]

Pseudo-resistant hypertension is defined as uncontrolled hypertension due to either inadequate measurements, atherosclerosis or poor adherence to treatment, or insufficient drug doses. In some cases it was associated with white coat hypertension or non-adherence to treatment.[5,8] The identification of these factors is very important in order to reduce the risk of adverse events related to renal denervation.[9]

The prevalence of hypertension varies significantly; in clinical studies, it was found to be around 12–18%, but after excluding the pseudo-resistant cases, the real prevalence was established at 5% in the general population and slightly higher in hypertension centers.[3,10]

Recent studies have proved that the incidence of hypertension varies by race and gender, being higher in the non-Hispanic black population and in women, especially the non-dipping blood pressure forms. Besides race, gender, or associated comorbidities, one of the most important contributors to the development of resistant hypertension is the sympathetic nervous system.[1]

The renal sympathetic nerves are located within and adjacent to the renal artery wall,[9] and the sympathetic nervous system plays an important role in renal physiology. Sympathetic activation triggers renal arterial vasoconstriction, which leads to the stimulation of renin secretion with increased sodium and water reabsorption and increased blood pressure.[2,5] This overexpressed sympathetic activation is more pronounced in the younger population.[8]

Current guideline recommendations regarding the use of renal denervation/ablation as a therapeutic strategy are controversial. The 2017 guidelines of the American College of Cardiology (ACC) and the American Heart Association (AHA), and the 2018 guidelines of the Canadian Cardiovascular Society do not recommend this procedure effective in reducing blood pressure, and the 2018 guidelines of the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH) do not recommend it for the routine treatment of high blood pressure due to the lack of necessary evidence regarding safety and efficacy (recommendation class III, level B). However, these guidelines assert that invasive therapeutic methods, including renal denervation or the stimulation of baroreceptors, can be used as effective therapeutic approaches in case of pharmacological failure (recommendation class II, level B).[1]

EFFECTIVENESS OF RENAL ABLATION – WHAT DO WE KNOW AND WHAT IS NEW?

Renal ablation represents an invasive technique used as an alternative for the treatment of resistant hypertension. In the last decade, several studies have analyzed its efficacy in the treatment of resistant hypertension. However, the results vary widely, from a significant reduction of ambulatory systolic blood pressure to an insignificant effect on blood pressure reduction.[2] These differences can be explained by incorrect blood pressure measurement techniques, the different classes and doses of the drugs used to treat hypertension, and the different response of each patient to drug therapy.[1,2]

The most important clinical trials that have studied the efficacy of renal ablation are SYMPLICITY HTN-2, HIT-ON MED, SPYRAL HTN-OFF MED, and RADIANCE-HTN SOLO.[1,2]

Results from the SYMPLICITY HTN-2 study, performed on a sample of 106 patients, have shown a reduction in blood pressure of 31/12 mmHg in patients with renal denervation, compared with 0/–1 mmHg in patients using only drug therapy.[5]

SYMPLICITY HTN-3 (2014), the first renal denervation trial, did not reveal significant differences between the invasively treated group (renal ablation procedure) and the control one. However, further analyses have exposed not only significant problems regarding the study design (non-homogeneous study population), but also a low level of experience in the study centers, with uncontrolled adherence to treatment and uncontrolled changes in the pharmacological treatment, as well as the use of a wide range of antihypertensive classes and several types of ablation catheters.[1,8]

The more recent clinical trials, SPYRAL HTN-ON MED, SPYRAL HTN-OFF MED, and RADIANCE-HTN SOLO, have all considered these parameters, and their results have demonstrated a statistically significant diminution in ambulatory blood pressure and systolic office blood pressure.[1]

SPYRAL HTN-ON MED is a global multicenter, blinded (patient and evaluator), randomized, chess-controlled study that evaluated not only the efficacy of renal ablation, but also the safety of this technique in the treatment of un-

controlled hypertension despite maximal treatment with antihypertensive agents.[1] The trial, conducted between July 2015 and June 2017, included 80 patients from 25 clinical centers. The results concluded that renal denervation is associated with a statistically and clinically significant reduction of blood pressure between the groups, three months after the procedure. Also, the trial did not report any adverse safety effects associated with renal denervation.[1,2]

SPYRAL HTN-OFF MED is a multicenter, single-blind, randomized controlled study regarding the efficacy of renal denervation, conducted in 21 centers. There were 353 patients enrolled, aged between 20 and 80 years, and one of the particularities of the study was the continuation of oral drug therapy for at least three months. The results showed a significant blood pressure reduction in the group treated interventionally.[11]

RADIANCE-HTN SOLO is also a global multicentric, single-blind, randomized, sham-controlled trial that aimed to evaluate the efficacy of renal denervation using the endovascular ultrasound technique.[1] Between March 2016 and December 2017, 146 patients aged 18–75 years, with a proper renal anatomy for this technique (renal anatomy was assessed using CT angiography or magnetic resonance before randomization), were enrolled from 21 centers.[1] The main purpose of the study was to demonstrate the effectiveness of this therapeutic technique for the treatment of uncontrolled hypertension without concomitant medication. The results proved that endovascular denervation reduces significantly the systolic and diastolic blood pressure at two months following the procedure. It was also observed that this effect was not influenced by age, gender, ethnicity, geography, or baseline blood pressure variations. The average reduction of systolic blood pressure was 8.5 mmHg, 6.3 mmHg greater than the reduction in the controlled group. However, efficacy and safety of this treatment should be established beyond a period of two months, especially regarding the safety of discontinuing antihypertensive drugs for longer periods.[1,2,12]

RADIOSOUND-HTN was the first trial in which renal denervation has been performed using three different procedural approaches – denervation at the main renal arteries, at the main renal arteries and side branches, and ultrasound denervation. The results have strengthened previous research, proving once again that renal denervation is able to decrease blood pressure significantly.[11] Regarding the most efficient invasive technique, endovascular ultrasound-based renal denervation was found to be superior to the other two techniques. Still, long-term follow-up has shown no comparable differences between the groups regarding the rate of response to renal denervation.[13]

The experimental study performed by Fink *et al.* on animals did not find a significant clinical pattern of blood pressure reduction after bilateral renal denervation.[14] These results were also confirmed by Grisk O., who concluded that the use of new techniques may reduce the degree of renal re-innervation, but the beneficial effects of bilateral renal denervation may be due to over-sensitivity to denervation.[15]

In a study conducted on hypertensive mice with chronic renal disease, Nishihara *et al.* have proved that renal denervation has an antihypertensive effect by increasing urinary sodium excretion in the early phase, followed by increased GABAergic input into the hypothalamic paraventricular nucleus in the late phase. These results were also sustained in diabetic rats or with renal kidney disease.[16]

RENAL DENERVATION: PROS AND CONS

Given the controversial results of clinical studies, several questions were raised regarding the efficacy and safety of the renal denervation technique. Preclinical studies on animal models have shown that renal denervation is effective in reducing high blood pressure, and the reduction is maintained several weeks after surgery. On the other hand, this beneficial effect could not be sustained, even in younger mice. Moreover, studies have shown that renal denervation has beneficial effects also on target organs including systolic left ventricular function, bioavailability of nitric oxide, or carbohydrate metabolism.[2]

The efficacy and safety of renal denervation were also demonstrated in a meta-analysis performed by Dahal *et al.*; however, the authors consider the short follow-up periods of the included studies a major limitation.[6]

A closer analysis of the studies in which renal denervation has not proven his effectiveness suggests that treatment with oral antihypertensive drugs must be continued after the procedure in order to achieve an adequate level of systolic blood pressure. In addition, patients with moderate uncontrolled blood pressure are not suitable for this type of treatment.[2]

Another main disadvantage of renal denervation is the fact that its blood pressure-reducing effect is not uniform among hypertensive patients. Also, it was observed that being part of a non-African population, age under 65 years, a more efficient glomerular filtration rate at the baseline, or the use of aldosterone antagonists increase adherence to treatment. According to the Austrian Transcatheter Renal Denervation Registry, female and non-diabetic patients are also more responsive to the treatment.[4,17]

Furthermore, an important factor that can modify the efficiency of renal denervation is the number of performed ablations. i.e. the operator's experience.[7]

Results of the studies performed so far have shown a possible efficacy of renal denervation in case of heart failure or arrhythmias, but further studies are needed to validate these results.[18]

CONCLUSIONS

Although, initially, renal denervation had been highly appreciated, further clinical trials have considered it insecure due to the lack of evidence regarding its efficiency and safety. In the present, there are numerous promising data that underscore the advantages of using this technique. Still, current guidelines do not recommend to perform this technique as routine, and the therapeutic decision is based on the operator choice and experience, respectively on the patient's profile.

CONFLICT OF INTEREST

Nothing to declare.

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CLINICAL UPDATE

OBSTETRICS AND GYNECOLOGY // INTENSIVE CARE

Acute Fatty Liver of Pregnancy

Lucian Gheorghe Pop[1], Ioan Dumitru Suciu[2], Nicolae Suciu[1,3], Oana Daniela Toader[1,3]

[1] National Institute of Mother and Child Care, Bucharest, Romania
[2] Department of General Surgery, Floreasca Emergency Hospital, Bucharest, Romania
[3] "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

CORRESPONDENCE

Lucian Gheorghe Pop
Str. Gheorghe Polizu nr. 38-52
Bucharest, Romania
Tel: +40 741 044 720
E-mail: popluciangh@icloud.com

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ABSTRACT

Acute fatty liver of pregnancy (AFLP) is a rare but life-threatening condition that develops in the third trimester of pregnancy. AFLP shares similar clinical features with other more common pregnancy-associated conditions. However, early correct diagnosis is important for maternal and fetal survival. Once the diagnosis has been established, immediate delivery and maternal intensive support should be undertaken. Both parents and the infant should be tested for deficiencies of the mitochondrial fatty acid oxidation, especially for long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency, as many cases of AFLP are related to disruption of this physiological enzymatic pathway.

Keywords: acute fatty liver of pregnancy, long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency, Swansea criteria, newborn metabolic screening

INTRODUCTION

Acute fatty liver of pregnancy (AFLP) usually presents after 30 weeks of gestation, it has an incidence of about 1 in 15,000 pregnancies[1] and is a potentially lethal condition, for both mother and baby. It is characterized by a lack of necrosis and inflammation, although there is a large fatty penetration of hepatocytes at a microvesicular level. Risk factors include first pregnancy, co-existing diagnosis of other liver diseases – including preeclampsia (PE) –, male fetus, and multiple gestations.[1]

DIAGNOSIS

Clinical features consist of nausea and vomiting, abdominal pain, fatigue, polydipsia, and polyuria, as well as jaundice with rapid progression to acute liver failure. The associated complications include encephalopathy, coagulopathy, hypoglycemia, and renal failure. Laboratory findings include elevated liver enzymes, hyperbilirubinemia, hyperuricemia, hyperammonemia, and hypoglycemia.[1]

The differential diagnosis of AFLP includes several maternal diagnoses such as PE, hemolysis, elevated liver enzymes, low platelet count (HELLP) syndrome, and intrahepatic cholestasis of pregnancy (IHCP). In all four conditions,

Ioan Dumitru Suciu • Calea Floreasca nr. 8, 014461 Bucharest, Romania. Tel: +40 724 556 862, E-mail: i.d.suciu@yahoo.com

Nicolae Suciu • Blv. Eroii Sanitari nr. 8, 050474 Bucharest, Romania. Tel: +40 744 525 913, E-mail: nsuciu54@yahoo.com

Oana Daniela Toader • Blv. Eroii Sanitari nr. 8, 050474 Bucharest, Romania. Tel: +40 722 347 000, E-mail: oana.toader@yahoo.com

there is an elevation in liver enzymes and hyperbilirubinemia. In PE there is hypertension and proteinuria, and in severe cases, abdominal pain, headache with visual disturbance, and thrombocytopenia. HELLP syndrome is a life-threatening condition that manifests with proteinuria with or without hypertension, thrombocytopenia with hemolysis, abdominal pain, and headache. The predominant features of IHCP are pruritus, jaundice, and high serum bile acids. Even if the differential diagnoses can be present by themselves, in about 30% of women with AFLP there is accompanying PE or HELLP syndrome.[1]

The gold standard method for the positive diagnosis of AFLP is liver biopsy and the demonstration of microvesicular fatty infiltration.[2] However, liver biopsy is seldom performed and potentially dangerous, especially in the presence of coagulation disorders. Consequently, the diagnosis is usually made by application of the Swansea criteria,[3] which combine clinical and laboratory markers. A positive screening result for AFLP is given if at least six of the following are present: abdominal pain, vomiting, polyuria/polydipsia, encephalopathy, hyperbilirubinemia, low glucose levels, hyperuricemia, hyperammonemia, raised white cell blood count, ascites or intense liver image on ultrasound scan assessment, high transaminases values, renal injury, coagulopathy, and hepatic microvesicular steatosis (Table 1).

ETIOLOGY

Advances in molecular technologies suggest that AFLP may be caused by dysfunctional mitochondrial processes in both the mother and the fetus.[4] In the mitochondria, there is a pathway specialized in achieving energy from free fatty acids – the fatty acid oxidation (FAO) pathway, which becomes active when glycogen stores are depleted, during fasting and ketogenesis. The by-products of FAO can be used by the brain, heart, liver, and skeletal muscles in lack of glucose. The process of FAO requires several steps in order to be accomplished. The fatty acids are first transported by special carriers to the mitochondrial inner membrane, where they are split in a cascade of four enzymatic processes.

Shortage of the third enzyme, long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD), leads to abnormal and potentially toxic levels of medium- and long-chain fatty acids. This condition is the consequence of an autosomal recessive (AR) disorder and, in its heterozygous state, has been diagnosed in some pregnant patients with AFLP, while in its homozygous state can be diagnosed in some of their babies.[5,6] The enzyme deficiency is most commonly caused by a mutation in the alpha-unit of the tri-functional protein gene where guanine is replaced by cytosine in position 1528, which alters amino acid 474 from glutamic acid to glutamine (E474Q). This mutation is identified in 65% to 90% of LCHAD-deficient patients.[7] As the mutation is AR, it should not, in normal conditions, cause anomalous fatty acid oxidation in the mother. Nevertheless, when both the father and the mother are heterozygous for the mutation, the fetus could acquire the abnormal genes from both, and would, therefore, be incapable of metabolization of long-chain fatty acids.

The fetal unmetabolized free fatty acids flow back through the placenta to the mother's blood, straining the maternal liver function and overwhelming the already reduced hepatic enzyme activity, ensuing the appearance of clinically visible AFLP.[8] Postnatally, the metabolic hepatic strain in the mother lowers and explains why the maternal FAO ultimately comes back to normal in the postpartum period.[9] Keeping this hypothesis in mind, babies delivered from mothers with AFLP should always be checked for abnormalities of FAO. Otherwise, LCHAD deficiency would probably be diagnosed later in infancy, when its consequences could be irreversible. In LCHAD-deficient infants, toxic by-products of FAO can build up in the mitochondria and can lead to degeneration and fatty infiltration of the skeletal and cardiac muscle fibers. There can also be hepatomegaly and liver dysfunction because of lipid deposition, jaundice, and progressive impairment of the bilirubin metabolism. LCHAD deficiency can also lead to sud-

TABLE 1. Swansea criteria for the probability of acute fatty liver of pregnancy[1,3]

Six or more of the criteria below should be considered diagnostic of AFLP in a woman with no other liver conditions of pregnancy (PE or HELLP)
• Vomiting
• Encephalopathy
• Polydipsia/polyuria
• Abdominal pain
• Bilirubin more than 0.8 mg/dL
• Elevated urea above 950 mg/dL
• Hypoglycemia less than 72 mg/dL
• Leukocytosis more than 11,000/mL
• Ascites
• ALT values above 42 U/L
• Ammonia values above 66/µmol
• Coagulation function or prothrombin time more than 14 seconds
• Acute kidney injury or creatinine more than 1.7 mg/dL
• "Intense liver" on ultrasound image
• Microvesicular steatosis on liver biopsy

den infant death, especially when the infants experience severe fasting or vomiting, making them metabolically dependent on gluconeogenesis from the lipid metabolism.[10]

The recurrence of AFLP is documented with subsequent pregnancies, and the theoretical risk is 25%, but in clinical practice, just several cases have been reported. Genetic testing for a fetus in future pregnancies can be offered if mutations in the parents are known.[8]

PROGNOSIS AND MANAGEMENT

AFLP may lead to extremely severe consequences for both the mother and the fetus. Early recognition of the condition with delivery and full supportive maternal care are extremely important for the outcomes of both mother and child. The postpartum course of the mother largely depends on the early recognition of AFLP – the time from the development of the first symptoms to delivery.

Recent data report a decrease over time in maternal and fetal mortality associated with AFLP, as we have come to understand more about the condition. Early diagnosis is of utmost importance as it carries an increased risk of maternal and fetal mortality and morbidity, with 2% maternal and 11% fetal reported death rates.[2]

The principles of treatment for AFLP involve three key steps: timely diagnosis, rapid delivery, and thorough maternal care, which are the pillars of survival in AFLP. Laboratory results in AFLP do not always match the gravity of the condition; therefore, suspicion of AFLP and a low threshold of admission for patient monitoring should be undertaken. Before delivery, the mother should be stabilized by a comprehensive and experienced team that can offer airway support, hypertension treatment, and correction of hypoglycemia, coagulation, and electrolyte function. The care of these patients should be provided by specialists in intensive care, gastroenterology, and perinatology. Continuous infusion of intravenous fluids and blood, assessment of vital signs, and evaluation of mental health are also utterly important. Fetal assessment is also crucial prior to delivery. Delivery should be achieved upon stabilization of the mother. Vaginal birth is not contraindicated in AFLP and should be tried if the maternal situation allows it. In clinical practice, however, delivery by caesarean section is often chosen as the maternal function is deteriorating fast. Postnatally, women that have suffered from AFLP should be closely monitored for bleeding as they can suffer from severe coagulopathy. Disseminated intravascular coagulopathy is often the presenting symptom of AFLP (90%), and it might be severe. Intraabdominal hemorrhage is a serious negative feature in pregnancy-related liver disease and is common regardless of the way of delivery.[11,12] Seldom is it possible that this patient might present non-obstetric hemorrhage such as Mallory-Weiss rupture, a conditions that requires interventional therapies. Transfusion of blood products and fluids is often needed.[13,14] Hypoglycemia is another important consequence that can develop in AFLP, and glucose infusion may be needed. Pancreatitis has been reported in some affected patients, with devastating consequences – infections and retroperitoneal bleeding, especially in the setting of coagulopathy. Maternal serum amylase and lipase, and imaging examinations, such as computed tomography and magnetic resonance, may be valuable in examining pancreatic involvement.[15] Encephalopathy can be the very first symptom and in the setting of AFLP can quickly progress to cerebral edema, convulsions, and coma.[16] Cases of diabetes insipidus have also been reported. Hypothetically, this is due to raised values of vasopressinase that metabolizes arginine vasopressin.[17]

Anesthesia in AFLP is a challenge as there are multiple pathologies involved in these patients, and currently there are no protocols and only scant guidelines. It has to be customized to the patients' need, and it might require blood transfusion, vasopressors, and electrolyte replacement. Multidisciplinary management is mandatory to manage this critical patient.[18]

In severe cases, liver transplantation has been performed for AFLP. This topic remains controversial as in some cases women on the waiting list were removed following improvement of their hepatic function and complete recovery. Auxiliary liver transplantation with keeping the native liver in situ and removal of the transplanted liver after full recovery has been reported.[16,18] However, in a retrospective study Kushner *et al.*[19] have shown that women undergoing liver transplant for AFLP had a lower outcome compared with women of the same age who had a transplant for acute liver failure. Survival graft at 5 years was lower among pregnant women, which might be explained through a higher rejection rate during pregnancy.

CONCLUSION

As seldom as it is, acute fatty liver of pregnancy remains a life-threatening condition that develops toward the last part of the pregnancy. Early diagnosis, though difficult because of the features shared with other more common pregnancy-associated conditions, is the cornerstone for maternal and fetal survival. Immediate delivery and maternal intensive support should be undertaken. Both parents and the infant should be checked for deficiencies in the fatty acid oxidation, especially for LCHAD deficiency.

CONFLICT OF INTEREST

Nothing to declare.

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4. Panteghini M. Recommendations on use of biochemical markers in acute coronary syndrome: IFCC proposals. eJIFCC 14. http://www.ifcc.org/ejifcc/vol14no2/1402062003014n.htm (28 May 2004)

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