Treatments used in menopausal women susceptible to dyslipidemia and diabetes

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Abstract

Objective: The objective of this study was to investigate the efficacy of types of treatment most used in menopausal women with dyslipidemia and susceptible to insulin resistance. **Material and Methods:** In the period between 2006 and 2016, articles of the PubMed database were evaluated using the keywords: *pancreas, menopause, dyslipidemia* and *treatment*. The following parameters were evaluated: title, year of publication, author, country of origin, studied model (human or animal), types of analysis (biometric, biochemical, physiological, morphological and immunohistochemical). **Results:** Of 530 articles investigated, 11 were evaluated, among which 45% used physical exercise as a treatment, 37% used the pharmacological treatment and 18% used diet. As for the year and country where the study was performed, 73% of the articles were published in the last six years (2011-2016), and 73% were published in the United States. In 27.3% of the articles were used animal models, and 72.7% used human models. The most employed analysis in the studies was the biochemical, and the least used (5%) was the morphological. **Conclusion:** Although physical exercise was the most common treatment in this study, the other treatments (diet and drugs) are of paramount importance to prevent pancreatic diseases and the development of type 2 diabetes, which certainly trigger a clinical picture of dyslipidemia, resulting in the irreversible deterioration of pancreatic cells.

Keywords: pancreas, dyslipidemia and diabetes, physical exercise, treatment.

1 Introduction

Aging is a natural process of individuals development that occurs gradually. It involves biological, functional, structural, chemical, environmental and sociocultural factors, such as quality of life, diet, sedentary and physical activity, which are closely linked to the healthy or pathological aging. Biological factors such as functional decline of cells promote continuous imbalance of hormonal regulatory systems that produce metabolic and physiological changes, leading to reduction of functional reserves and making the elderly more prone to diseases (INSTITUTO…, 2010; SALLIS, 2000).

According to estimates of the World Health Organization (ORGANIZAÇÃO…, 2013) in 2020 we will have a greater number of older people in relation to children aged under five years. In 2060, 25% of the population will be over 65 years, of which 55% will be women.

Policies of prevention and treatment are indispensable tools because aging is characterized by a functional decline resulting from decreased aerobic capacity and progressive weakness of body muscles that are accentuated from the age of 50, the period coinciding with the menopause that greatly affects the elderly's quality of life (AL-NUAIM, MIRDAD, AL-RUBEAAN et al., 1997; AKAHOSHI, SODA, NAKASHIMA et al., 2001; GRAFF-IVERSEN, THELLE and HAMMAR, 2008).

Menopause is characterized by inactivity of ovaries and consequent deprivation of estrogen. It represents the beginning of a new phase of women's lives around the age of 45-55 years. In addition, there is a trend to body mass gain, and women are susceptible to changes in lipid metabolism, increasing the levels of total cholesterol, lipoproteins and triglycerides, and reduction of HDL-cholesterol levels, leading to a highly favorable to atherogenesis lipid profile, especially when associated with diabetes and hypertension (GRAFF-IVERSEN, THELLE and HAMMAR, 2008; STACHOWIAK, PERTYNSKI and PERTYNSKA-MARCZEWSKA, 2015).

It is known that cholesterol is a precursor in the formation of female sex hormones. Thus, with deprivation of estrogen, there is an increase of remnant cholesterol, consequently increasing low-density lipoproteins (LDL), very low-density lipoproteins (VLDL) and triglycerides (TG), resulting in a highly favorable to atherogenesis lipid profile. Excess fatty acids in circulation contribute to the accumulation of these lipids in the adipose and muscle tissue, promoting weight gain in the body, liver and pancreas (GRAFF-IVERSEN, THELLE and HAMMAR, 2008; FARIA, CORREIA-JUNIOR, ANJO et al., 2013; STACHOWIAK, PERTYNSKI and PERTYNSKA-MARCZEWSKA, 2015; PANDEY, CHAWLA and GUCHHAIT, 2015).

Pancreas is an essential organ to maintain energetic homeostasis, and in a clinical picture of dyslipidemia, it produces insulin (hypoglycemic) and glucagon (hyperglycemic) with

the function of balancing the blood sugar concentration. In cases of excess lipids in the blood, the pancreas tries to balance the hyperglycemia by increasing the insulin production (β-cells). The chronic state leads to exhaustion that impairs the function of β-cells and develops a pre-diabetes condition. Excess cholesterol leads to lipotoxicity in pancreatic β-cells, causing apoptosis, and leading to decreased insulin production (LIU and MAUVAIS-JARVIS, 2010). Such clinical picture associated with estrogen deficiency can be a determining factor in changing the pre- and postmenopausal profile (WU, FANG, ZHENG et al., 2013)

Dyslipidemia is a factor of risk and disease in cases of pancreatic dysfunction, therefore, the first line of action must include its prevention for premenopausal and postmenopausal women looking for different types of treatment. Studies have pointed that physically active individuals enjoy a better quality of life and have lower mortality rates, resulting in greater longevity (MATSUDO and MATSUDO, 1992; ANTUNES, SANTOS, CASSILHAS et al., 2006)

It is extremely important to know how to prevent the physiological and endocrine changes caused by deprivation of ovarian hormones in menopausal women to encourage their aging with quality of life and well-being.

Thus, the aim of this study is to identify the types of treatments used in menopausal women predisposed to dyslipidemia and diabetes.

2 Methods

The search was performed in the PubMed electronic database because this is a complete source that includes the journals of Medline, Pre-Medline and Health STAR. The following descriptors were used randomly: "pancreas" and "dyslipidemia" and "exercise" and "menopause" and "treatment" (Table 2). Only articles published in the last 10 years, from 2006 to 2016 were surveyed. The aim was to analyze the methods of treatment used in menopausal women with dyslipidemia.

The initial analysis included the surveyed titles. Then, the articles were separated per proximity of the proposed theme. The abstracts were read, ensuring that the articles chosen for reading in full met the following inclusion criteria: studied model (animal or human), type of treatment, analyzed parameters (biometric, biochemist, physiological, immunological and morphological), year and country of publication of the articles. The following were excluded: review articles, book chapters, dissertations, theses, conference proceedings and government reports.

The articles were selected according to the established criteria to show the treatment used in the pancreatic diseases in menopausal women with dyslipidemia.

3 Results

Analyzing the selected articles, it appears that different types of treatment are prescribed to the elderly, such as hormone replacement, dietary supplements, diet, drugs and physical exercise, to reach benefits and reverse processes of dyslipidemia, pointing to reduced LDL levels, thus preventing the development of diabetes and improving quality of life (ALMEIDA, PITANGA, FREITAS et al., 2012; KITABCHI, MCDANIEL, WAN et al., 2013; OMIYA, MINAMI, SATO et al., 2015; AMARAL, LIMA, ORNELAS et al., 2015).

In total, 530 articles were found, and 11 articles were selected for further analysis (Tables 1 and 2).

Regarding the year and the country where the study was performed, 73% of the articles were published in the last six years (2011-2016), and the United States is leader in number of publications, with eight articles (73%), followed by England with two publications (18%), and Netherlands with one publication (9%) (Table 2).

All selected articles used human or animal models in menopause, with dyslipidemia and relating the pancreas as the target organ. Of the 11 articles, 27.3% used animal models and 72.7% used human models. Note that 36.4% of the studies used menopausal women and 18.2% used ovariectomized rats.

Analyzing the studies in humans, we found that in 50% of the articles were used biochemical, biometric, physiological and immune parameters for analysis and in the other 50% were used biochemical, biometric and physiological parameters. In the animal model, we found that 33% used only biochemical and immunological parameters, while 67% analyzed the biochemical, biometric, physiological, immunological and morphological parameters. Despite this, the biochemical analysis was the most used in the total number of articles, and the least used was the morphological with only 5% (Figure 1).

The most used types of treatments in menopausal women with dyslipidemia were physical exercise (45.4%), diet (18.2%) and pharmacological (36.4%). In relation to articles using physical exercise, in 60% was employed aerobic exercise, in 40% was used combined exercise (aerobic and anaerobic), and in 18.2% was used diet (Figure 2).

The Table 3 shows the types of treatments and the principals results found in the articles studied.

4 Discussion

Most of selected articles were published in American journals (73%). The article by Malin, Solomon, Blaszczak et al. (2013) stands out because it shows an epidemic of obese people, about 79 million pre-diabetic individuals, and the urgency

Table 1. Number of total articles by descriptor and per exclusion criteria. Period of 2006-2016.

		Key words			Articles	Selected
Pancreas	Exercise	Menopause	Dyslipidemia	Treatment	0	0
Pancreas	Exercise	Menopause	Dyslipidemia		0	0
Pancreas	Exercise	Menopause			0	0
Pancreas		Menopause			29	1
Pancreas			Dyslipidemia	Treatment	187	2
Pancreas	Exercise		Dyslipidemia	Treatment	4	3
Pancreas	Exercise				310	5

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of taking measures given the estimate of development of type 2 diabetes by 30% of this population. The second country with largest number of publications was England (18%), and the articles had reports of the difficulty faced with reducing the rate of pre-diabetic people (MALIN and KIRWAN, 2012).

With menopause, there is decline of estrogen levels and is established metabolic imbalance, which leads to weight increase, consequently increasing lipids in the circulation of blood vessels (dyslipidemia), resulting in oxidative stress and insulin resistance (IR). Studies on these changes are quite significant

in order to ensure improved quality of life because women live a third of their lives in pre- and postmenopausal phases.

Based on this information, we will discuss the main treatments used by menopausal women prone to dyslipidemia and predisposed to diabetes.

4.1 Diet treatment

Menopausal women in search of a better quality of life see the diet as an alternative for reducing the symptoms caused by the effects of menopause.

Table 2. General index of selected articles mentioning the author's name, year of publication, Authors' country and Country of publication.

Title	Author	Year	Authors' country	Country of publication	Model	Treatment	Analyzed parameters
Impaired β-cell function attenuates training effects by reducing the increase in heart rate reserve in patients with myocardial infarction.	Omiya, Minami, Sato et al.	2015	Japan	Holland	Human	Exercise	Biometric, biochemical, physiological, immunological
17 β-estradiol protects against glucosamine-induced pancreatic β-cell dysfunction.	Kang, Chen, Wu et al.	2014	Japan	United States of America	Animal	Pharmacological	Biochemical, immunological
DHEA supplementation in ovariectomized rats reduces impaired glucose-stimulated insulin secretion induced by a high-fat diet.	Veras, Almeida, Nachbar et al.	2014	Brazil and South Africa	England	Animal	Pharmacological	Biometric, biochemical, physiological, immunological and morphological
Adverse association between obesity and menopause in mice treated with bezafibrate, a pan peroxisome proliferator-activated receptor agonist.	Faria, Correia-Junior, Anjo et al.	2013	Brazil	United States of America	Animal	Pharmacological	Biometric, biochemical, physiological, immunological and morphological
Pancreatic β-cell function increases in a linear dose-response manner following exercise training in adults with prediabetes.	Malin, Solomon, Blaszczak et al.	2013	United States of America	United States of America	Human	Exercise	Biometric, biochemical, physiological
Pancreatic β-cell function is a stronger predictor of changes in glycemic control after an aerobic exercise intervention than insulin sensitivity.	Solomon, Malin, Karstoft et al.	2013	France	United States of America	Human	Exercise	Biometric, biochemical, physiological
Effects of high-protein versus high-carbohydrate diets on markers of β-cell function, oxidative stress, lipid peroxidation, proinflammatory cytokines, and adipokines in obese, premenopausal women without diabetes: a randomized controlled trial.	Kitabchi, Mcdaniel, Wan et al.	2013	United States of America	United States of America	Human	Diet	Biometric, biochemical, physiological

Table 2. Continued...

| Title	Author	Year	Authors' country	Country of publication	Model	Treatment	Analyzed parameters
Fasting hyperglycaemia blunts the reversal of impaired glucose tolerance after exercise training in obese older adults.	Malin and Kirwan	2012	United States of America	England	Human	Exercise	Biometric, biochemical, physiological, immunological
Effects of soy protein and isoflavones on glycemic control and insulin sensitivity: a 6-mo double-blind, randomized, placebo-controlled trial in postmenopausal Chinese women with prediabetes or untreated early diabetes.	Liu and Mauvais-Jarvis	2010	China	United States of America	Human	Diet	Biometric, biochemical, physiological, immunological
Effects of exercise training intensity on pancreatic beta-cell function.	Slentz, Tanner, Bateman et al.	2009	United States of America	United States of America	Human	Exercise	Biometric, biochemical, physiological, immunological
Effects of raloxifene on insulin sensitivity, beta-cell function, and hepatic insulin extraction in normal postmenopausal women	Nagamani, Szymajda, Sepilian et al.	2008	United States of America	United States of America	Human	Pharmacological	Biometric, biochemical, immunological
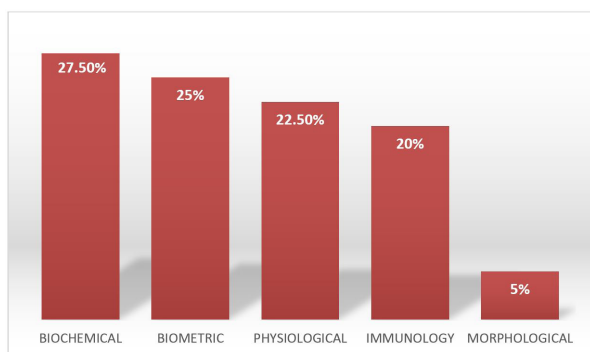
Figure 1. Percentage of biochemical, biometric and physiological parameters analyzed in the selected articles.
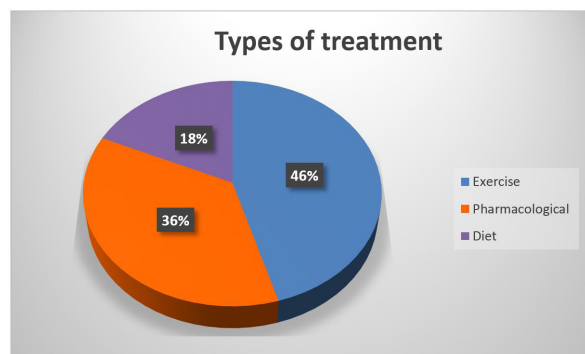

Figure 2. Types of treatment: Diet, Pharmacological and Physical exercise.

Analyzing articles related to diet (Table 2), we found that 50% of these articles were of premenopausal obese women using different types of diets. With this approach, Kitabchi, Mcdaniel, Wan et al. (2013) has compared diets rich in carbohydrate (HC) and protein (HP). It found that HP diets promoted decrease in inflammation, oxidative stress, lipid peroxidation, and inflammatory cytokines, and improved functions of β-cells and insulin sensitivity, preventing cardiovascular diseases, compared to a high carbohydrate diet (HC). On the other hand, Liu and Mauvais-Jarvis (2010), has compared diets containing soy protein and isoflavones, and concluded that the values related to insulin sensitivity and glycemic control were similar. However, it was observed that the soybean group (soy protein with isoflavones) obtained a reduction in 2 hours and 6 hours post-glucose load tests (PG-2h-6h). Given the results found, further studies on the subject are key because the presented diets are nutritionally similar.

4.2 Pharmacological treatment

Of the 11 selected articles, 36% used pharmacological intervention, of which 100% were human model studies, 83.3% used biochemical, biometric and physiological analysis, and 16.7% used immunohistochemical analysis, as shown in Table 2.

Note that 75% of the articles mention the benefits of drug therapy while preserving the pancreatic islets and decreasing insulin resistance (NAGAMANI, SZYMAJDA, SEPILIAN et al., 2008; VERAS, ALMEIDA, NACHBAR et al., 2014), reducing lipid levels (triglycerides and cholesterol), and consequently lowering insulin levels (FARIA, CORREIA-JUNIOR,

ANJOS et al., 2013). However, Kang, Chen, Wu et al. (2014) emphasizes the side effects of some drugs that possibly induce resistance to insulin, apoptosis of β-cells, thereby developing type 2 diabetes.

Continuous use drugs occasionally may have their therapeutic effects decreased, requiring periodic adjustment of the dose to achieve an effective result. However, when combining continuous use drugs with regular exercise practice, the quality of life is

Table 3. General index of selected articles mentioning the chosen treatment and the results.

Exercise treatment	Results
Combination (Aerobic and Anaerobic)	Improved the β-cells function; Improved VO2; ↑ High density lipoproteins (HDL); ↓ Low density lipoproteins (LDL); ↑ Insulin sensitivity; ↓ Insulin secretion; ↓ Weight; ↓ TG. ↑ Function of β-cells; ↑ VO2max; ↑ Cardiovascular fitness; ↑ Insulin sensitivity; ↓ Fasting glucose
Aerobic	↓ Insulin secretion; ↓ Visceral adipose tissue; ↓Triglycerides; ↓ Weight; ↓ BMI; ↓ Compensatory insulin secretion; ↓ Insulin secretion; ↓ GSIS

Pharmacological treatment	Results
Glucosamine (Osteoarthritis)	↓ Insulin secretion; ↓ Influx of Ca2+; ↓ Insulin mRNA expression. ↑ Apoptosis of β cells; ↑ Size of the islets; ↑ ER stress-related protein.
Dehydroepiandrosterone (DHEA)	↓ Insuline secretion ↓ IR (insulin resistance); ↑ Estrogen; ↑ AKT (kinase protein); ↑ I.S. (insulin sensitivity).
Bezafibrate (lipid-lowering)	↓ Body mass; ↓ Insulin levels; ↓ Hypertrophy of the islets; ↓ Diameter of the islets; ↓ Mass of the islets; ↓ HOMA-IR. (insulin resistance); ↑ Fasting glucose.
Raloxifene	↓ Cholesterol; ↓ Low density lipoproteins (LDL); ↓ Hepatic extraction of insulin.

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Table 3. Continued...

Exercise treatment	Results
Diet	**Results**
	HP diet (proteins):
	↑I.S.(insulin sensitivity);
Hypocaloric protein (HP) and	↑Function of β-cells;
Hypocaloric carbohydrate (HC)	↓Oxidative stress;
	↓Inflammatory markers;
	↓Cardiovascular risk factors.
	Soybeans:
Soybeans and Isoflavone	Improved insulin secretion induced
	by postload glucose

improved by reducing the need for periodic adjustments as majority indication of physicians of all specialties.

4.3 Physical exercise treatment

Of the 11 articles analyzed (Table 2), 45% used physical exercises as intervention method, and 100% of such interventions were performed in humans, divided in 60% using aerobic exercises and 40% using the combination of aerobic and anaerobic exercises.

All articles not only confirm, but also emphasize the beneficial effects of exercise as a non-pharmacological treatment for the improvement of lipid profile and weight loss, thus reversing the clinical picture of dyslipidemia, preventing pancreatic function by the decreased biosynthesis and secretion of insulin, normalization of the function of β-cells, thus avoiding a possible condition of type 2 diabetes. Consensus among many authors is that aerobic exercise in mild or moderate intensity was more effective in preserving the pancreas, preventing its function from exhaustion and leading to reversal of the clinical picture of dyslipidemia (SLENTZ, TANNER, BATEMAN et al., 2009; KANG, CHEN, WU et al., 2014).

5 Conclusion

Analyzing the selected articles, it´s clear that physical exercise alone or combined with other treatments is the most used in menopausal women with dyslipidemia and susceptible to insulin resistance, because this type of intervention does not favor side effects. Diet is widely used as a first line of prevention, but needs further study. We highlight the association of drug treatment with regular physical exercise practice to favor the reduction of drug dosages or even polypharmacy. It is consensus that the use of multiple drugs may increase the risk of adverse side effects.

There are few studies observing morphoquantitative changes in different cells of the pancreatic islets. Many of the articles analyzed the relationship of treatments with biochemical changes (levels of triglycerides, LDL, HDL, HOMA IR, HOMA% β-cell, OGTT), biometrical changes (weight, BMI) and physiological changes (blood pressure, VO_2), but studies linking these changes to morphological changes in the cells that form the pancreatic islets are scarce.

The main conclusion of this study is that all kinds of treatments used in menopausal women with dyslipidemia, no matter if diet, drugs or physical exercise, are crucial for the prevention of pancreatic diseases, preventing the development of type 2 diabetes and the progression of dyslipidemia.

Conflict of interest

The author(s) declare(s) that there is no conflict of interest regarding the publication of this paper.

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