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Effects of Breast Cancer and Type 2 Diabetes Mellitus on Ventilation Volumes and Pressures in Adult Women

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ABSTRACT

Background and objective: Type 2 diabetes mellitus (DM2) and breast cancer (BC) are diseases of high prevalence worldwide. Both alter lung function separately. So suffering both tables would increase this decrease in lung function. The objetive was to determine the effects of DM2 and BC on ventilation volumes and pressures in adult women.

Material and Methods: Forty-two women patients were recruited, of whom 40 were accepted under the exclusion criteria. They were divided into four groups: control group (CG), DM2, BC and DM2+BC. Body plethysmography was used to measure forced vital capacity, lung volumes, airway resistance and muscle pressures. Finally the normality of the data was determined using Student's t test or the Mann-Whitney U test; the threshold of significance was $p<0.05$.

Results: No significant differences were observed in the anthropometric variables between the control group and the other groups. The ventilation flows showed no significant differences, while the lung volumes presented significant differences in the inspiratory capacity (IC) variables ($p<0,002$). Maximum inspiratory and expiratory pressures (MIP-MEP) also presented significant diminution ($p<0,001$; $p<0,041$, respectively).

Conclusions: From the results obtained we can conclude that the combination of type 2 diabetes mellitus with breast cancer caused a diminution in ventilation volumes and pressures, specifically in IC, MIP and MEP.

Keywords: diabetes mellitus, breast cancer, pulmonary volumes.

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INTRODUCTION

Diabetes mellitus has been rising world-wide. According to figures from the International Diabetes Federation, 425 million people presented diabetes during 2017 and a figure of around 629 million cases is projected for 2045 [1]. Progression of the symptoms is slow and a large number of people suffer the pathology for many years without being diagnosed; it is estimated that 1 out of 2 adults is in this situation [1,2].

The figures published by the World Health Organization (WHO) for 2012 recorded 8.2 million deaths due to cancer and 14.1 million new cases of this pathology in the whole world. In this context, breast cancer is the second most common type in the world and the most frequent in women, with an incidence of 1.67 representing 25% of all cancers in this population [3].

A strong association has been observed between the increase of comorbidities and diabetes sufferers [4]. One example of this is the fact that patients with diabetes are at greater risk of breast cancer [5,6]. In this situation, diabetes is able to promote more rapid tumour growth mediated by hyperglycemia, insulin resistance and hyperinsulinemia [7,8]. All these events may predispose women with diabetes to a greater risk of more advanced breast cancer at the moment of diagnosis.

Diabetes causes various microvascular complications attributable to biochemical and structural changes in the proteins of the basal membrane of different organic systems. Specifically, at the alveolar level it restricts lung volumes and capacities [9]. This

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functional deterioration has been found principally through transversal associations between the state of the patient's diabetes and measurements of forced vital capacity (FVC) and forced expiratory volume in the first second (FEV_1); reductions have been found in these variables in association with type 1 and type 2 diabetes [10]. Furthermore, autonomic neuropathies affecting the phrenic nerves have been found, resulting in a reduction of muscular tone and diaphragm control [11].

At the same time, the use of radiotherapy and/or chemotherapy in addition to medical treatment are fundamental for the treatment of breast cancer. The former consists in local treatment to try to destroy the cancerous cells by the application of external or internal radiation [12]. In the latter, medications are administered which have a variety of secondary effects, particularly dyspnea [13,14]. In general, these treatments cause pneumonitis and fibrosis, which have an impact on lung function [15]. Verbanck *et al*. (2012) evaluated the acute effects on the respiratory function associated with conventional radiotherapy in 26 breast cancer patients at the start of treatment and after 3 months; they observed a significant reduction in the FEV_1, the FVC and the free diffusion of carbon monoxide (FDCO) [16].

As diabetes and breast cancer produce different effects on lung function, as shown separately, we hypothesised that patients with both pathologies present a poorer lung function than patients who present only one of these conditions. The object of the present study was therefore to determine the effects of breast cancer and type 2 diabetes mellitus on ventilation volumes and pressures in women in the city of Talca.

MATERIALS AND METHODS

Study design: Analytical cross-sectional cohort study in which a non-probabilistic sample was selected by subject convenience, subject to inclusion and exclusion criteria.

Patients: Forty women of the Maule Region, Chile, with diagnosis of diabetes mellitus and/or breast cancer, with both pathologies being treated currently. The sample was divided into four groups of 12 women each: control (CG), diabetes mellitus (DM2), breast cancer (BC) and diabetes mellitus plus breast cancer (DM2+BC). The women in the CG were selected from the Geriatrics Service of the Talca Hospital, Chile, where they attended for Preventive Health Check-ups. The women in the DM2 group had a certified diagnosis of type 2 diabetes mellitus, were being controlled by the Internal Medicine Service of the Talca Hospital and were undergoing treatment with metformin in doses of 500 to 750 mg/day. The patients in the BC group were being treated at the Oncology Service of the same hospital. They presented diagnosis of stage IIA to IIIc BC, bilateral or unilateral radical mastectomy and were undergoing adjuvant treatment, starting chemotherapy with doxorubicin, cyclophosphamide and paclitaxel two weeks after the mastectomy, and radiotherapy with doses of 50 Gy six weeks after the surgical procedure. For the DM2+BC group, patients were selected who met the above inclusion criteria for the DM2 and BC groups concomitantly. The exclusion criteria were: not presenting a chronic or acute respiratory disease at the time of evaluation, not being a habitual smoker, not presenting deformities in the thorax (Figure 1). The confounding variables (age, weight, height and body mass index) were contrasted with a statistical method to determine differences between the groups and ensure comparability (Table 1). This study forms part of a Lung

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Function Evaluation Project of the Physiotherapy Department which has been approved by the Scientific Ethics Committee of Universidad Católica del Maule (resolution 23/2016).

Evaluation of lung function: Measurements in all the tests followed the norms of the American Thoracic Society (ATS). Once the subject's age, height (SECA®220) and bodyweight (SECA® 840) had been recorded, she remained sitting quiet and relaxed for at least 10 minutes before the evaluation. The tests were carried out by a trained operator using a body plethysmograph (Mediagraphics, Model Platinum Elite DL®).

Forced Vital Capacity: Briefly, the patient ventilated through the pneumotachograph with normal volume for five respiratory cycles; she was then told to carry out a maximum inspiratory manoeuvre followed by maximum forced expiration. The best test out of a minimum of three acceptable and reproducible manoeuvres was selected [17].

Measurement of the maximum inspiratory and expiratory pressures (MIP-MEP): To evaluate the MIP, the nose clip was placed on the patient's nose. She ventilated to normal volume for five respiratory cycles through the mouthpiece and was then asked to carry out maximum expiration; the pneumotachograph was blocked and she was asked to carry out maximum inspiration against the closed valve. For the MEP, the instruments were placed in the same position. The patient ventilated to normal volume for five respiratory cycles through the mouthpiece and was then asked to carry out maximum inpiration; the pneumotachograph was blocked and she was asked to carry out maximum expiration against the closed valve. In each case, the best test out of a minimum of three acceptable and reproducible manoeuvres according to current norms was selected [18].

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Ventilation volumes: The mouthpiece was adjusted to the patient's height. The patient had to ensure that her mouth remained engaged with the mouthpiece during the test to avoid air leakage; this was done by holding her facial muscles with her hands during the evaluation. Then the cabin was closed and the patient was asked to carry out four ventilations at normal volume. She was instructed to “pant gently”, trying to move volumes of between 50 and 60 mL. The requested panting frequency was around 60 per minute (1 Hz). The professional in charge activated the shutter for 2 to 3 seconds, then told the patient to to take a maximum inspiration followed by expiration to residual volume (RV)[19].

Analysis: The results were analysed using Excel (Microsoft Office, 2010) to tabulate the data and Graph Pad Prism 6® (GraphPad Software Inc., 1995-2015) for statistical analysis; the data were presented as means with standard deviation. The first statistical process was to determine the normality of the data using the Shapiro-Wilk test. Comparisons were carried out using ANOVA or the Kruskal Wallis test; Tukey's test or Dunn's test were used respectively to analyse the difference between variables. The level of significance was $p<0.05$.

RESULTS

Of the 50 patients selected, 48 met the criteria for inclusion in the study, CG: n=12, DM2: n=12, BC: n=12, DM2+BC: n=12. Two patients were excluded as habitual smokers (Figure 1). No significant differences were observed in age (p=0,704), weight (p=0,052), height (p=0,278) or body mass index (BMI) (p=0,361) between the groups (Table 1). In the

evaluation of lung function, the lung flows presented no significant differences (Table 2). The MIP presented significant differences between CG and DM2 ($p<0,01$), and similar differences were observed between CG and BC ($p<0,01$) and between CG and DM2+BC ($p<0,01$). The MEP only presented significant differences between CG and DM2+BC ($p<0,05$) (Table 3). Significant differences in lung volumes were only found in the IC, where there were significant differences between CG and DM2 ($p<0,05$), between BC and DM2+BC ($p<0,01$) and finally between CG and DM2+BC ($p<0,05$) (Figure 2).

DISCUSSION

The object of this investigation was to observe the behaviour of lung pressures and volumes when two currently frequent conditions are associated, namely DM2 and BC. The results obtained enabled us to observe that patients with both conditions (DM+BC) suffer a significant diminution of MIP, MEP and IC compared to the CG. There are two reasons why this is important: i) There is a direct relation between lung pressure and volume, so a higher MIP suggests an increased IC and vice-versa, consistent with the results obtained (Figure 2) [20]; and ii) The IC is recruited in activities outside everyday behaviours. It is known that the increase in ventilation demand is sustained by the IC, so any reduction translates into a fall in the maximum oxygen consumption during maximum effort tests with resulting appearance of dyspnea [21].

The MIP and MEP of the DM2 group were lower than those of the CG. This agrees with the findings reported by Fuso *et al.* (2015), who monitored lung function associated with glycemia control (GC) in subjects with DM2 by measuring baseline lung volumes and

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pressures, and the values after 3 months of GC. They observed that the MIP diminished in patients with poor GC, and increased in those with good GC; however the difference between the two groups was not significant (p = 0.091). The MEP diminished both in patients with poor GC and those with good GC; again the difference between the two groups was not significant (p = 0.719) [22]. The results obtained also showed a diminution of the MIP and MEP of the BC group in comparison with the CG, however this was not significant. In contrast, Dos Santos *et al*. (2013) studied the effect of radiotherapy in BC on lung function, assessing 20 women before and after treatment; they determined that there was a significant diminution of MIP and MEP at the end of the period [23]. Likewise, O'Donnell *et al*. (2016) found a significant diminution in the MIP of women with BC as compared to the control group [24]. In this context, we note two important facts: i) The behaviour of MEP differs from that of MIP, for which statistical differences were only observed in the CG. This is due to the double function of the abdominal muscles, which are a fundamental part of the coughing mechanism [25] – their tone fluctuates constantly depending on posture [26]; and ii) the results obtained for MIP-IC presented a diminution which expresses the proposed relation between them, supported by the observations of Fadil *et al.* (2015), who determined a parallel reduction between pressures and volumes in subjects with DM2 [27]. Investigations in mice with DM showed diminished capillarisation and angiogenesis in the skeletal muscle, resulting in smaller fibre size and muscle belly; in the long term these alterations will generate a reduction in muscle functioning [28]. Another important phenomenon which is relevant in this context is the existence of diabetic neuropathy; this condition diminishes muscle mass significantly compared to subjects with neuropathies but who do not suffer DM. The association of neuropathy with diabetes accelerates the process of muscular atrophy [29].

Specifically, muscular atrophy in DM derives from a diminution in everyday activity and deregulation in the protein synthesis pathway. This is because energy storage and the mitochondrial function are reduced, accelerating the loss of muscle proteins. At the same time, defects in some substrates of the insulin receptor (IRS)-1/phosphatidylinositol-kinase (PI3K) would lead to a reduction in the daily glucose consumption and insulin use by the tissues. This would increase the degradation and diminution of muscle protein synthesis via PI3K/Akt [30]. Furthermore, it has been shown that cancer increases insulin resistance, aggravating this lower activity in the protein synthesis pathways [31]. We hypothesise that, in addition to this mechanism, the increase in RV may also contribute to this diminution in MIP. It is known that increased RV provokes a diminution in the IC and a lowering of the diaphragmatic cupula [20]; this creates an inappropriate environment for generation of force by the diaphragm, limiting its capacity for incursion. Although the results obtained do not show significant differences in the RV, an increased value is observed in the DM2+BC group. This agrees with the findings reported by Connolly and Mittendorfer, who say that ultrasound allows diaphragm dysfunctions to be measured in real time through diaphragm movement; ultrasound can also give an idea of muscle inspiratory pressure, as subjects with a smaller change in amplitude between inspiration and expiration in tranquillity would have a smaller diaphragmatic force [32]. This also correlates with lung function, specifically with the RV; an increase of the latter is associated with a diminution in the amplitude of change of the diaphragmatic cupula [33]. We assume this as a limitation of this study; at the same time, we raise the question of how to determine the real contribution of the two mechanisms to the diminution of MIP in patients with DM2+BC.

Lecube *et al*. (2010), investigating the assessment of lung volumes, explored the lung function in obese women with DM and found that patients with both conditions presented a significant diminution in VEF_1 and RV in comparison with obese women without DM. Furthermore, they showed no significant differences in total lung capacity (TLC) [34]; in this context, measurement of muscular force by MIP and MEP would have complemented the results reported and explained them better. Fadil *et al.* (2015) studied 45 men with DM2, finding a significant diminution in TLC as compared to CG [27]. The results obtained show a similar decline in lung capacities, specifically the IC of patients with DM which was not significant; however this variable was significantly smaller than the CG when the condition of BC was added (Figure 1). The evidence indicates that the IC is equivalent to between 50 and 60% of the TLC and that both are sensitive to restrictive patterns; this is important if we consider that Sreeram (2016), in a study of 90 subjects with DM2, showed the existence of a restrictive pattern in 55% of the cases [35].

The IC reached its lowest value in the DM+BC group. In this context, BC would also influence this variable; thus when the evidence concerning DM is examined, it is important to examine also the effects of BC on lung function. In this context, Muñoz *et al*. (2019), in a population of patients similar to that of the present study, showed that the IC was reduced in women with BC treated with chemotherapy and radiotherapy concomitantly [36]. O'Donnell *et al.* (2016) measured the behaviour of VO_{2max} and the lung function in patients with BC, finding a significant diminution in the percentage of the predicted IC of these patients versus the control group [24]. This result disagrees with the findings of the present investigation, where no significant differences were observed in this variable. However we did observe significant differences between BC and DM. Likewise, when BC is combined

with DM, a significant diminution was found compared to the CG, and we therefore attribute this greater diminution to the sum of the two conditions. This indicates that there are two phenomena acting in parallel on the respiratory system: on the one hand DM, which, as explained above, diminishes muscle mass and strength [28]; and on the other cancer and its treatment, which provoke various alterations in the ventilation system such as loss of pneumocytes and tensioactive agent, and the appearance of oedema in the basal membrane [23]. These changes in conjunction would reinforce one another, generating a greater diminution of IC as compared to the other groups.

Among the limitations of this investigation, we recognise that the patients were not evaluated for dyspnea and physical activity. In this context, we believe that it would be very advantageous for future investigations to apply scales to objectify this symptom, complemented with the six minute walking test to determine its relation with IC. The standardisation of the cancer patients was not regulated, as there were patients in the BC and DM2+BC groups both with and without radiotherapy. From the results obtained we can conclude that the combination of type 2 diabetes mellitus with breast cancer caused a diminution in ventilation volumes and pressures, specifically in IC, MIP and MEP.

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original draft preparation: R.M.C, D.C.V, M.E.C; supervision: R.M.C; project administration: R.M.C.

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TABLES

Table 1. Description of the control group and patients with breast cancer.

	CG	DM2	BC	DM2+BC	p value
N	12	12	12	12	
Age (years)	56±9	59±53	61±9	59±10	0,704
Weight (kg)	67.25±11.35	80.83±9.17	70.40±8.12	70.90±10.37	0,052
Height (cm)	155.60±4.66	1.61±0.09	156.3±6.12	155.8±6.66	0,278
BMI (kg/m^2)	27.67±3.72	30.85±2.46	28.88±3.39	29.40±5.28	0,361
Origin of cancer					
LB°			5 (50)	5 (50)	
RB°			5 (50)	3 (30)	
BB°			0 (0)	2 (20)	
Stage of cancer					
0			1 (10)	2 (20)	
I			1 (10)	1 (10)	
II A			3 (30)	2 (20)	
II B			1 (10)	3 (30)	
III A			1 (10)	2 (20)	
III B			1 (10)	0 (0)	
III C			1 (10)	0 (0)	
IV			1 (10)	0 (0)	
Chemotherapy (mean mg/doses/cycle)					
Doxorubicin			95/4/4 (100)	102/4/4 (90)	
Cyclophosphamide			991/4/4 (100)	1020/4/4 (90)	
Paclitaxel			130/9/3 (90)	159/10/4 (70)	
Radiotherapy (radiation/sessions)					
Dose			50 Gy/25 (40)	37 Gy/27 (50)	

N: number; **kg:** kilograms; **cm:** centimetres; **kg/m^2:** kilograms divided by metres squared, **LB:** left breast; **RB:** right breast; **BB:** bilateral. **Gy:** Gray.

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Table 2. Description of lung flows in the sample studied.

Variable	CG (n=12)	DM2 (n=12)	BC (n=12)	DM2+BC (n=12)	p value
FVC (L)	2.94±0.28	2.57±0.52	2.93±0.30	2.54±0.86	0,074
FEV_1 (L)	2.38±0.20	2.12±0.43	2.31±0.37	2.10±0.64	0,154
FEV_1/FVC (%)	81.36±5.03	82.60±3.68	78.30±7.16	84.30±5.27	0,110
FEF_{25} (L/s)	5.12±0.83	5.44±1.07	4.98±1.00	5.42±1.46	0,092
FEF_{75} (L/s)	1.14±0.35	0.87±0.35	0.90±0.33	0.91±0.27	0,235
FEF_{25-75} (L/s)	2.52±0.62	2.18±0.60	2.22±0.76	2.35±0.56	0,158
FEF max (L/s)	5.88±0.97	5.84±1.08	5.53±0.50	5.75±1.51	0,609

CG: control group; **DM2:** diabetes mellitus; **BC:** breast cancer; **DM2+BC:** diabetes mellitus + breast cancer; **FVC:** forced vital capacity; **FEV_1:** forced expiratory volume in the first second; **FEV_1/FVC:** ratio between the forced expiratory volume in the first second and forced vital capacity; **%:** percentage; **FEF_{25}:** forced expiratory flow at 25% of the forced vital capacity; **FEF_{25-75}:** forced expiratory flow at between 25% and 75% of the forced vital capacity; **FEF_{75}:** forced expiratory flow at 75% of the forced vital capacity; **FEF max:** maximum forced expiratory flow; **L/s:** litres divided by seconds; **L:** litres; **s**: seconds.

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Table 3. Description of the lung pressures in the sample studied.

Variable	CG (n=12)	DM2 (n=12)	BC (n=12)	DM2+BC (n=12)	p value
MIP (-cmH_2O)	77.67±22.04	66.00±23.57	73.70±27.80	58.80±36.04	0,001
MEP (cmH_2O)	87.83±18.27	84.60±25.98	71.00±28.64	65.80±23.95	0,041

cmH_2O: centimetres of water; **MIP:** maximum inspiratory pressures; **MEP:** maximum expiratory pressures; **CG:** control group; **DM2:** diabetes mellitus; **BC:** breast cancer; **DM2+BC:** diabetes mellitus + breast cancer.

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435 **Table 4.** Description of the lung volumes in the control group and patients with breast
436 cancer.

Variable	CG (n=12)	DM2 (n=12)	BC (n=12)	DM2+BC (n=12)	p value
SVC (L)	3.10±0.32	2.59±0.38	3.07±0.30	2.55±0.81	0,062
IC (L)	2.52±0.37	2.24±0.28	2.61±0.32	2.04±0.58	0,002
ERV (L)	0.43±0.26	0.34±0.27	0.46±0.17	0.50±0.31	0,178
VGT (L)	3.11±0.55	2.98±0.58	3.00±0.94	3.11±0.90	0,609
RV (L)	2.54±0.37	2.34±0.59	2.54±0.90	2.61±0.94	0,963
TLC (L)	5.34±0.54	4.93±0.58	5.62±0.90	5.16±1.16	0,320
RV/TLC	46.00±5.42	47.00±8.08	44.40±8.12	50.60±11.49	0,227
RAW (cmH_2O/L/s)	1.17±0.68	1.64±0.64	1.50±1.20	0.89±0.40	0,467
GAW (L/s/cmH_2O)	1.17±0.69	0.68±0.22	0.95±0.51	1.38±0.72	0,065
sRAW (cmH_2O*s)	4.39±2.68	5.44±1.94	4.97±2.75	2.96±1.05	0,059
sGAW (1/cmH_2O*s)	0.33±0.22	0.20±0.07	0.25±0.12	0.35±0.11	0,072

437 **SVC:** slow vital capacity; **IC:** inspiratory capacity; **ERV:** expiratory reserve volume; **RV:**
438 residual volume; **TLC:** total lung capacity; **L:** litres; **RV/TLC:** residual volume divided by
439 total lung capacity; **RAW:** airway resistance; **GAW:** airway conductance; **sRAW:** specific
440 airway resistance; **sGAW:** specific airway conductance; **cmH2O/L/s:** centimetres of water
441 divided by litres divided by seconds**;** **L/s/cmH_2O:** litres divided by seconds divided by
442 centimetres of water; **cmH_2O*s**: centimetres of water per second; **1/cmH_2O*s:** one divided
443 by centimetres of water per second.
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FIGURES

Figure 1. Flow chart of recruitment and measurements of the four groups designated

Figure 2. Behaviour of airway pressures and volumes and statistical differences in the sample studied.

: $p<0.01$; *: $p<0.05$. **MIP: maximum inspiratory pressures; **MEP:** maximum expiratory pressures; **IC:** inspiratory capacity; **cmH_2O:** centimetres of water; **L:** litres; **CG:** control group; **DM2:** diabetes mellitus; **BC**: breast cancer; **DM2+BC:** diabetes mellitus + breast cancer. **A.** Maximum inspiratory pressure; **B.** Maximum expiratory pressure; **C.** Inspiratory capacity.

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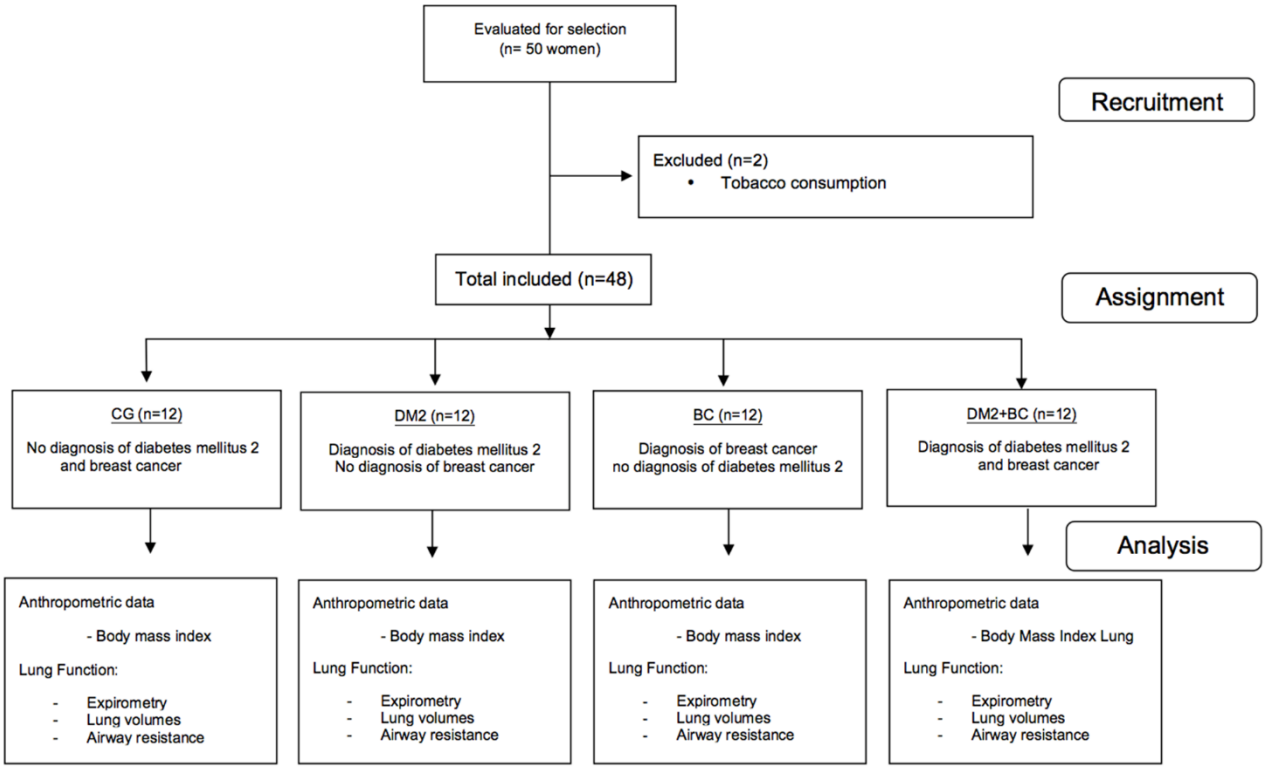

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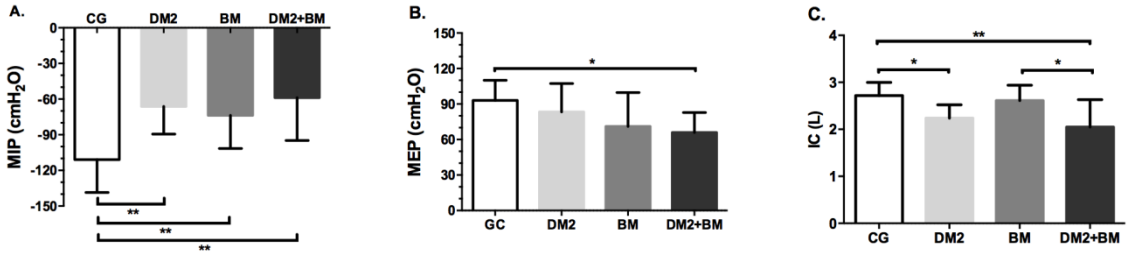

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