Article

Relationship between Osteoarthritis and Thyroid Dysfunction, as well as with Physical and Demographic Features

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Abstract

Osteoarthritis (OA) is a commonly prevalent and chronically complicated condition that affects different joints in millions of patients worldwide, leading to a cumulative effect over time. Due to few global prospective studies, this study investigated the association of OA to bodily and demographic characteristics of the study population. It demonstrated the levels of thyroid hormones in OA patients. Totally, 324 individuals; 162 normal (GN), 111 doubtful to minimal OA (GOA1) and 51 moderately to severe OA (GOA2) were subjected to this study from September to December (2021). For bodily characteristics of the study population, the findings of age, height and gender showed insignificance between study groups but not in weight and BMI.

Regarding demographic data, level of education, non-smoking and smoking, and non-arthritis and arthritis population were associated almost insignificantly with OA patients except for GOA2 patients, who showed a significant correlation to OA compared to GOA1 and GN. For chronic diseases, the association was observed insignificantly between GOA1, GOA2 and GN of 1 and 2 chronic diseases and between GOA1 and GN of 3 and 4 chronic diseases; however, significance was recorded in values of GOA2 in comparison with values of GOA1 and GN. For physical activity, significance was observed in low and high values but not in medium activities. Results without and with walking aids were variable significantly, in particular in values of GOA2 when compared to GOA1 and GN. Findings of TSH, T3 and T4 of GOA1, GOA2 and GN were correlated significantly. The association of TSH to the severity of OA revealed an obvious significance in values of crude, adjusted 1 and 2 models. In conclusion, this study was the first Iraqi report, and studies are necessary due to the significant association between OA and thyroid hormone dysfunction.

Keywords: OA, T3, T4, TSH, Risk factor, Iraq.

Introduction

OA is a commonly prevalent and chronically complicated condition affecting different joints in millions of patients worldwide, leading to a cumulative effect over time[1, 2]. Etiology is mainly unknown but is most likely multifactorial[3]. Several pathophysiological ways could be raised due to abnormal function in growth factors[4], protease inhibitors and proteolytic enzymes[5], reactive oxygen intermediates[6], neuropeptides[7], cartilage matrix fragments[8], cytokines[9] and prostaglandins[10].

These abnormalities lead to a cycle of degenerative processes in cartilages, bones, ligaments and synovial stratum to coincide with the inflammatory responses and increased sensitization in central and peripheral nervous systems[11,12]. OA has a dilemma; it usually starts attacking several joints long prior to middle age but cannot be detected till clinically becoming with symptoms many years later when anatomical structures of the joint are altered, and the disease is quietly developed[13]. However, the principle of OA morphology involves a slow-developed degenerative destruction of cartilages and the only episodic synovitis with alterations occurred in bones, synovial stratum and muscles [14,15].

The multifactorial natures of OA and the absence of reliable animal models will make discovering and developing new drugs even more challenging[16,17]. Also, complicated OA pathophysiologylogy calls for the biological system to dissect the molecular pathway of development of infection to decrease many efforts that focus on identifying and validating the disease models and biomarkers[18, 19].

The thyroid gland, a small shaped-like butterfly organ located around the trachea, plays a vital role in the body by making, storing and releasing several hormones, thyroxin (T4) and triiodothyronine (T3), which control body metabolism as needed. In addition to these hormones, the hypothalamus and the pituitary gland, located in the brain, help control the thyroid gland by releasing thyroid-releasing hormone (TRH) that stimulate releasing the thyroid-stimulating hormone (TSH) when the levels of thyroid hormones are too low or too high[20-22]. Thyroid hormones have potential roles in maintaining and remodeling bones and articular cartilages[23]. Genetically, many reports referred to the deiodinase-regulated local availability of active T3 hormone as potentially affecting maintaining and repairing cartilages[24-26]. Additional information referred that elevated intracellular T3 can increase the impact of the disease suggesting that decreased T3 availability in tissues could protect a joint from OA development [21, 27].

To date, few global prospective studies have demonstrated the levels of thyroid hormones in OA patients [28-31], whereas in Iraq, searching online processes failed to detect any further data. Hence, this study aimed to demonstrate the association of OA to bodily (age, weight, height, BMI and gender) and demographic (level of education, smoking, arthritis, chronic diseases, physical activity and use of walking aids) characterization of the study population, and hormonal thyroid dysfunction.

Materials and Methods
Ethical approval

The Scientific Committee licensed this study in the College of Medicine, University of Wasit (Iraq). Prior to collecting demographic data and blood samples, oral agreement was obtained from all study populations.

Study samples

A total of 324 individuals; 162 normal (GN), 111 doubtful to minimal OA (GOA 1) and 51 moderately to severe OA (GOA 2), from different areas in Wasit province (Iraq) were subjected to this study from September to December (2021).

After draining 3 ml of venous blood into a free-anticoagulant glass-gel tube, sera were obtained by centrifugation of blood samples (5000 rpm for 3 minutes) and kept in labeled Eppendorf tubes to measure thyroid hormones. Characteristics of the study population (risk factors) such as age, height, weight, body mass index (BMI), gender, education, physical activity, smoking, arthritis and other chronic diseases and use of walking aids were documented.

Laboratory estimation

A total automatic immunological analyzer, Cobas e411 system (Roche, Germany), was applied to detect the T3, T4, and TSH in the sera of the study population.

Statistical analysis

All obtained results were statistically analyzed by the GraphPad Prism (6.01) using the Chi-square ($x2$) and t-test to detect significant variation between study groups at $P<0.05$. Values of targeted markers and factors were expressed as mean ± standard deviation (M ± SD) or as percentage (%).

Results

Association of OA to bodily characteristics of the study population

The findings of the study population revealed that there were significant variations ($P<0.05$) in the values of study groups GN, GOA 1 and GOA 2 (Figure 1). For age, insignificant differences (P ± 0.05) were detected between the values of GN (58.1 ± 7.6), GOA 1 (57.9 ± 7.3) and GOA 2 (58.5 ± 8.3). Although insignificant variation (P ± 0.05) was seen between values of weight of GN (73.5 ± 9.1) and GOA 1 (74.9 ± 9.4), significant variation ($P<0.05$) was reported between values of GN and GOA 2 (78.6 ± 9.8) as well as between values of GOA 1 and GOA 2. Concerning the height of the study population, an insignificant correlation ($P>0.05$) was observed between values of GN (165.8 ± 6.5), GOA 1 (164.9 ± 5.2) and GOA 2 (165.8 ± 6.3). Significantly, the findings of BMI showed an elevation ($P<0.05$) in values of GOA 1 (27.5 ± 3.4) and more severely in GOA 2 (28.8 ± 3.6) when compared to GN (26.7 ± 3.3). Regarding gender, there were insignificant differences (P ± 0.05) between values of GN, GOA 1 and GOA 2 of females [99/162 (61.1%), 72/111 (64.9%) and 31/51 (60.1%), respectively] and males [63/162 (38.89%), 39/111 (35.14%) and 20/51 (39.22%), respectively].
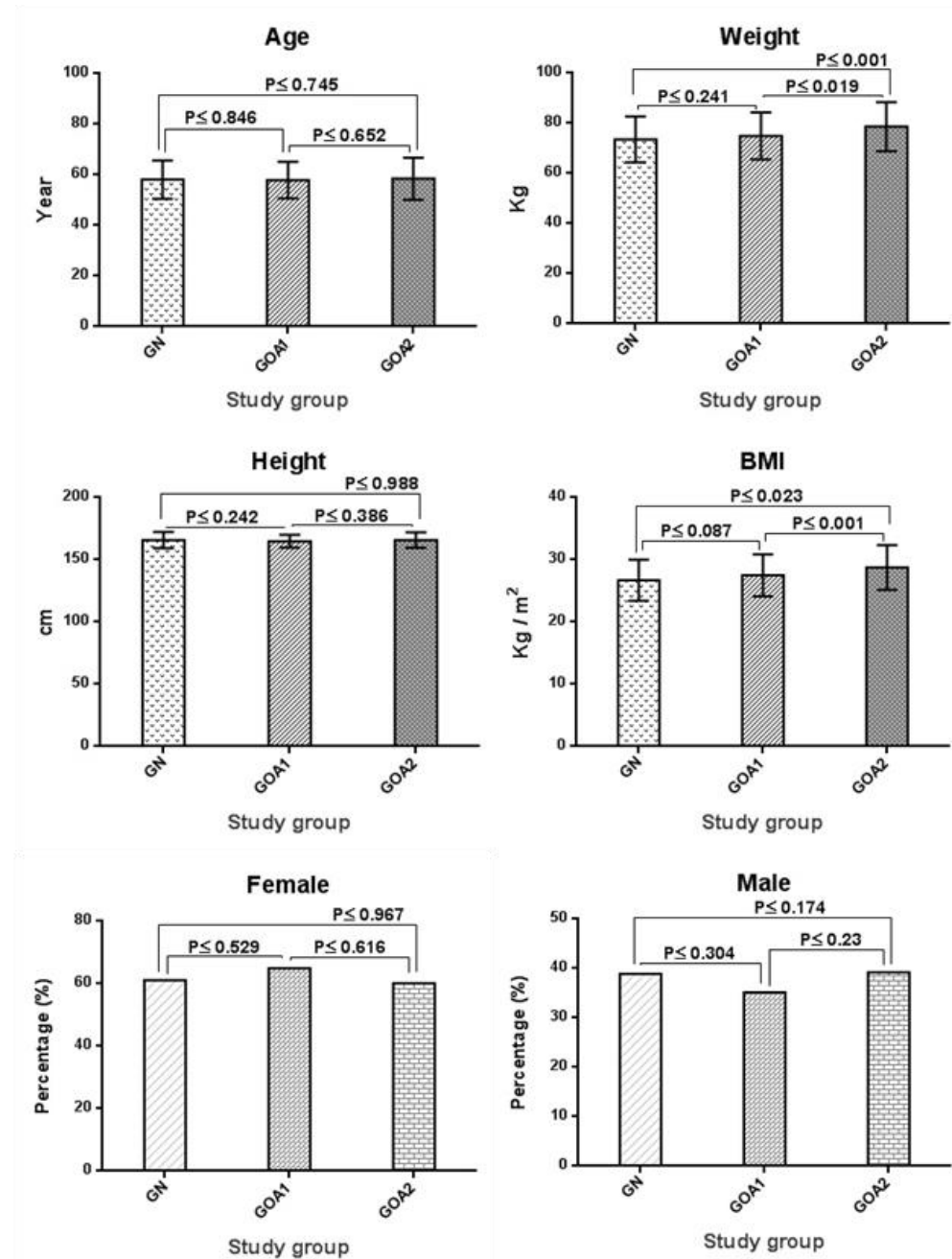
**Figure 1. Findings of bodily characteristics of the study population existed in GN, GOA1, and GOA2.**

Association of OA to demographic characteristics of the study population

Regarding the level of education, the findings of non-education individuals revealed insignificant differences (P>0.05) between values of GN [72/162 (44.4%)], GOA 1 [48/111 (43.2%)] and GOA 2 [23/51 (45.1%)] as well as between values of GOA 1 and GOA 2. These findings were similar to that detected in values of NG, GOA 1 and GOA 2 of both secondary [23/162 (14.2%), 15/111 (13.5%) and 9/51 (17.7%), respectively] and higher [15/162 (9.3%), 10/111 (9.1%) and 5/51 (9.9%), respectively] education. For primary education, no significant variation (P□0.05) was reported between values of GN [52/162 (32.1%)] and GOA 1 [38/111 (34.2%)] as well as with values of GOA 2 [14/51 (27.5%)], significant differences (P<0.05) were detected between values of GOA 1 and GOA 2 (Figure 2).
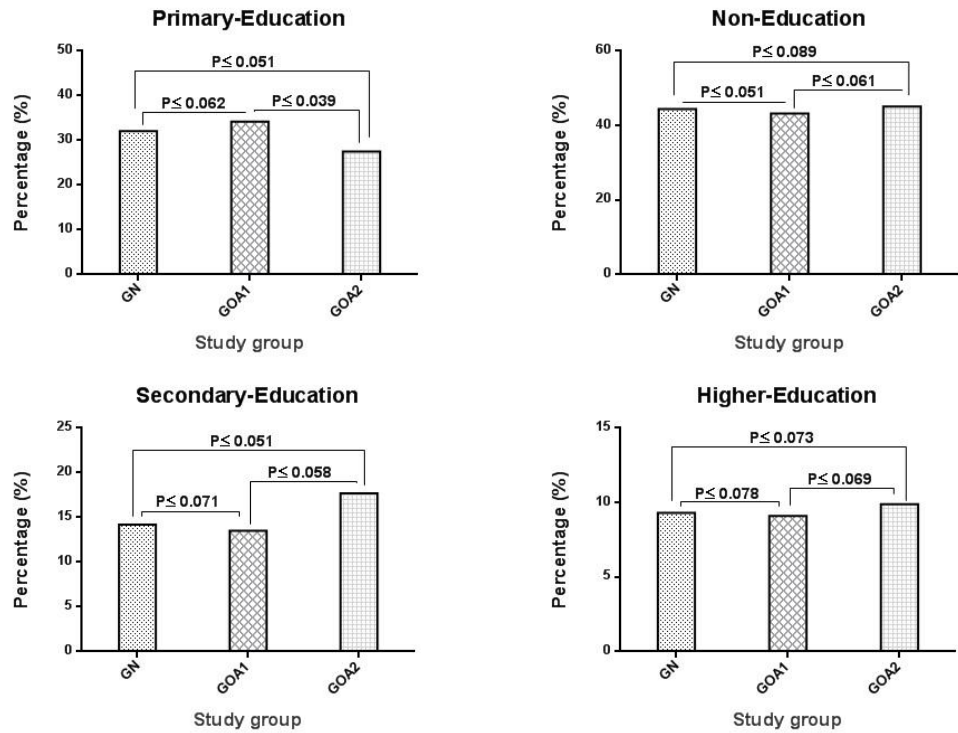
**Figure 2. Findings of the education factor of the study population existed in GN, GOA1 and GOA2.**

Additionally, comparative analysis between findings of categories of each education factor revealed a significant variation (P<0.05) between values of all study groups (Figure 3).
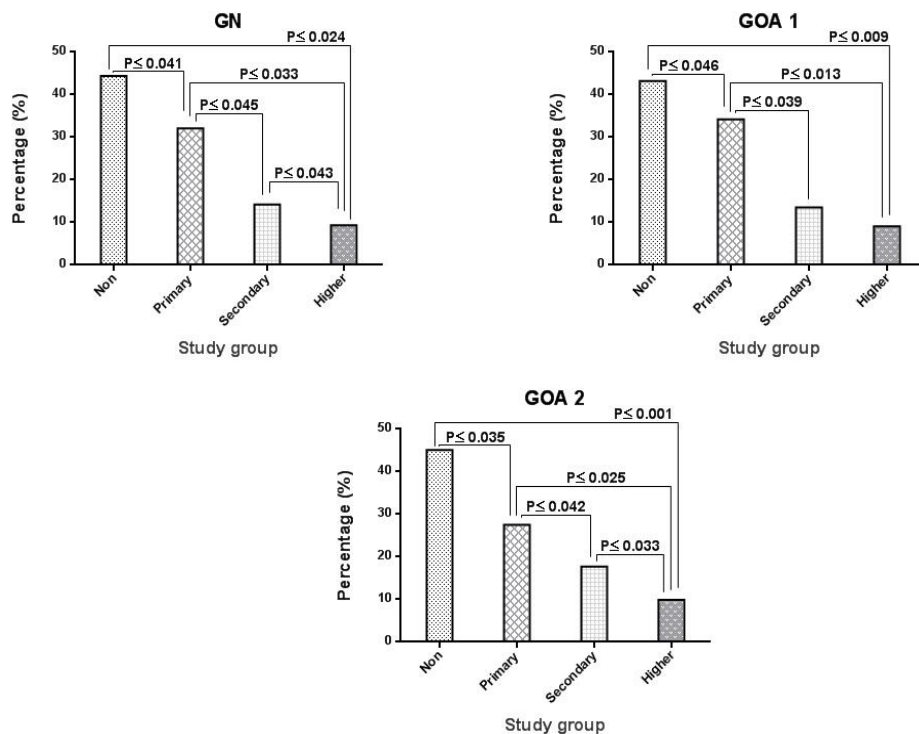
Figure 3. Results of categories of education factors among study groups (GN, GOA1 and GOA2).

The findings of the non-smoking study population showed that there was insignificant variation (P>0.05) between values of GN [114/162 (70.4%)] and GOA 1 [80/111 (72.1%)], but not between values of GN and GOA 2 [34/51 (66.7%)] as well as between values of GOA 1 and GOA 2 (P<0.05). In smoking individuals, the findings were similar to that detected in the non-smoking population as there

were significant differences (P<0.05) between values of GN [48/162 (29.6%)] and GOA 2 [17/51 (33.3%)] as well as between GOA 1 [31/111 (27.9%)] and GOA 2 (Figure 4).
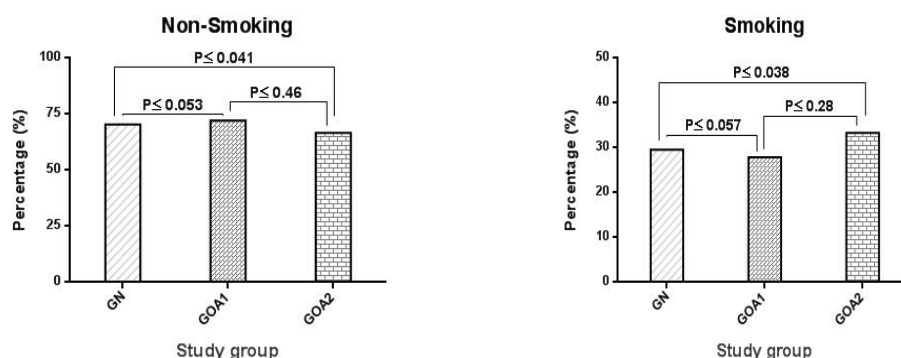
Figure 4. Findings of a smoking factor in the study population existed in GN, GOA1 and GOA2.

In non-arthritis and arthritis study population, insignificant association (P>0.05) was shown between the values of GN [124/162 (76.5%) and 38/162 (23.5%), respectively] and GOA 1 [84/111 (75.7%) and 27/111 (24.3%), respectively]; however, significant differences (P<0.05) were reported between values of GN and GOA 2 [31/51 (60.8%) and 20/51 (39.2%), respectively] as well as between values of GOA 1 and GOA 2 (Figure 5).
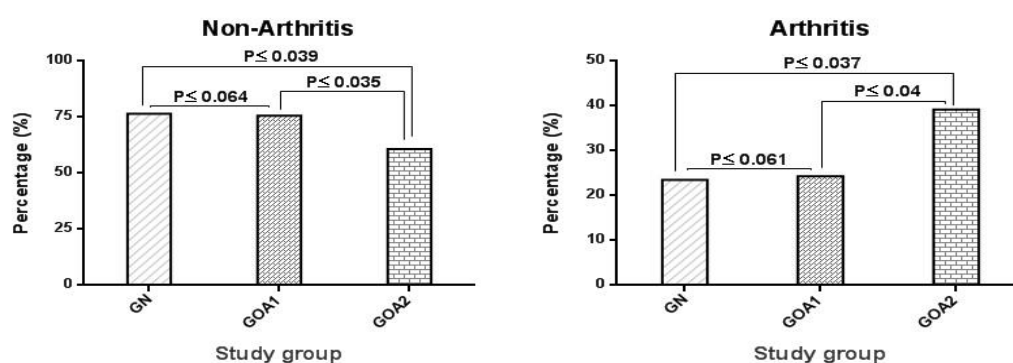
Figure 5. Findings of arthritis in the study population existed in GN, GOA1 and GOA2.

In this study, the findings of chronic diseases showed a significant variation (P<0.05) in association with the population of study groups (Figure 6). No-chronic diseases (0) were lowered significantly (P<0.05) in GOA 2 [5/51 (9.8%)] when compared to GN [47/162 (29.1%)] and GOA 1 [23/111 (20.7%)]; whereas, insignificant variation (P□0.05) was observed between values of 1 and 2 chronic diseases of GOA 1 [30/111 (27.1%) and 33/111 (29.6%), respectively], GOA 2 [12/51 (23.5%) and 15/51 (29.4%), respectively] and GN [44/162 (27.2%) and 43/162 (26.5%), respectively]. In categories of 3 and 4 chronic diseases, insignificant variation (P□0.05) was reported between values of GOA 1 [17/111 (15.3%) and 8/51 (7.2%), respectively] and GN [19/162 (11.7%) and 9/51 (5.6%), respectively]; however, there were significant differences (P<0.05) between values of GN and GOA 2 [12/51 (23.5%) and 7/51 (13.7%), respectively] as well as between GOA1 and GOA2.

Results of low physical activity showed there was a significant association (P<0.05) between the values of GOA 1 [66/111 (59.5%)] and GN [81/162 (50%)], GOA 2 [34/51 (66.7%)] and GN, and between values of GOA 1 and GOA 2. For individuals of medium physical activity, an insignificant association (P>0.05) was shown between values of GOA 1 [31/111 (27.9%)], GOA 2 [13/51 (25.5%)] and GN [47/162 (29.1%)]. However, the findings of the high physical activity popu-

lation revealed a significant correlation (P<0.05) between values of GOA 1 [14/111 (12.6%)], GOA 2 [4/51 (7.8%)] and GN [34/162 (20.9%)], (Figure 7).
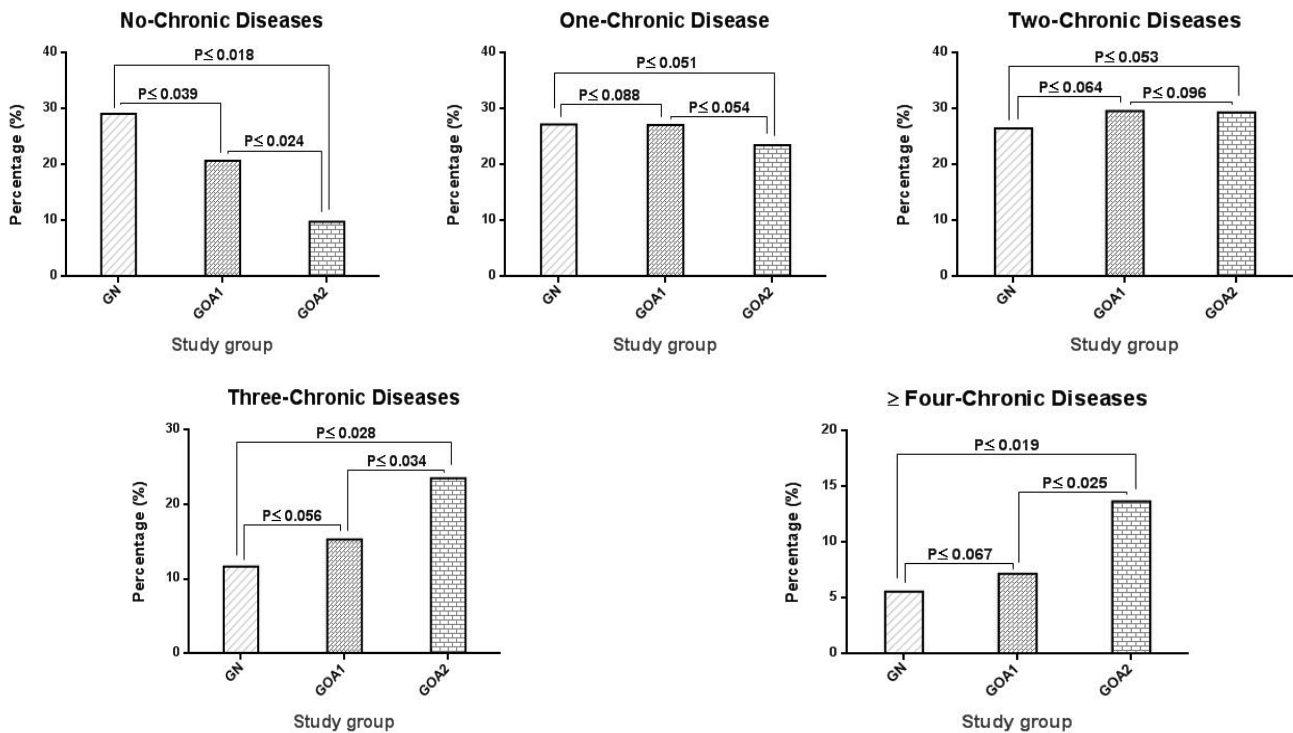

Figure 6. Findings of chronic diseases of the study population detected in GN, GOA1 and GOA2.
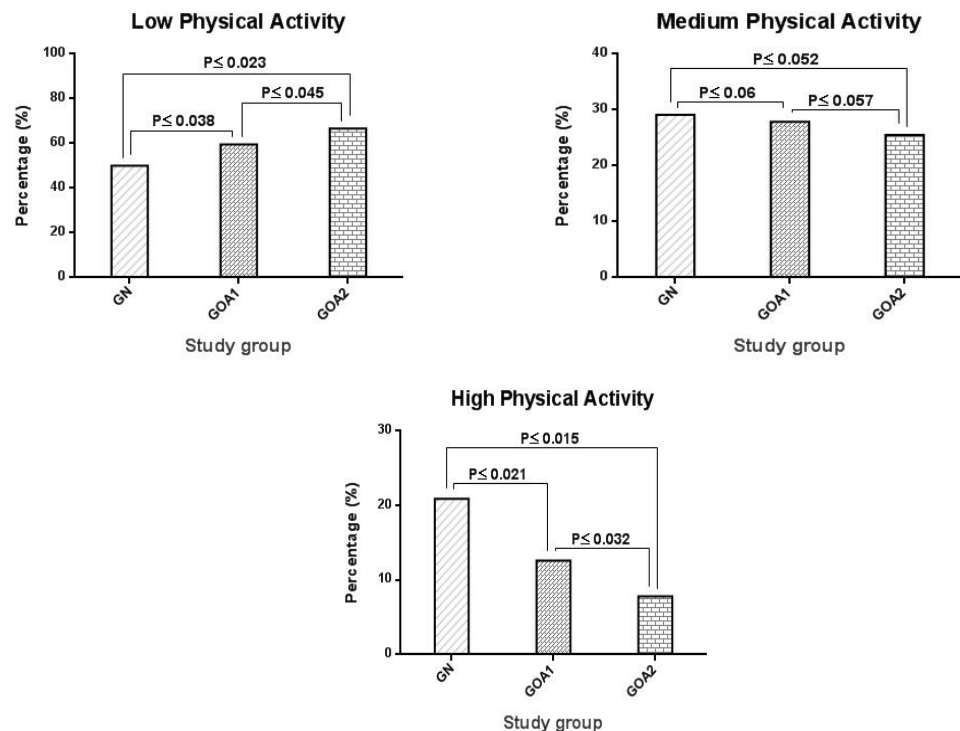
Figure 7. Findings of physical activity of the study population detected in GN, GOA 1 and GOA 2.

Statistically, no significant association (P□0.05) was reported between values of GOA 1 and GN in both without- [91/111 (64%) and 136/162 (83.9%), respectively] and with- [20/111 (18.2%) and 26/162 (16.1%), respectively] walking aids study population. However, values of GOA 2 of both without [33/51 (64.7%)] and with [18/51 (35.3%)] walking aids were associated significantly (P<0.05) with the

values of both GN and GOA 1. In comparison between values of with and without using aids, significant decreases (P<0.05) were observed in OA patients using walking aids (Figure 8).
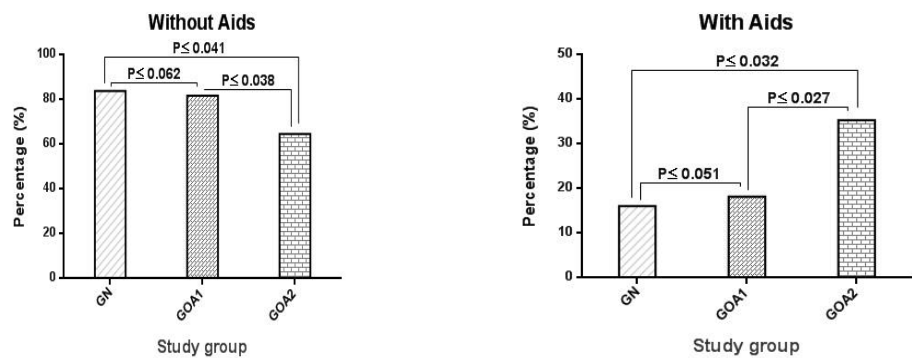
Figure 8. Findings of using walking aids among the GN, GOA 1 and GOA 2 study population.

Association of OA to levels of thyroid hormones of the study population

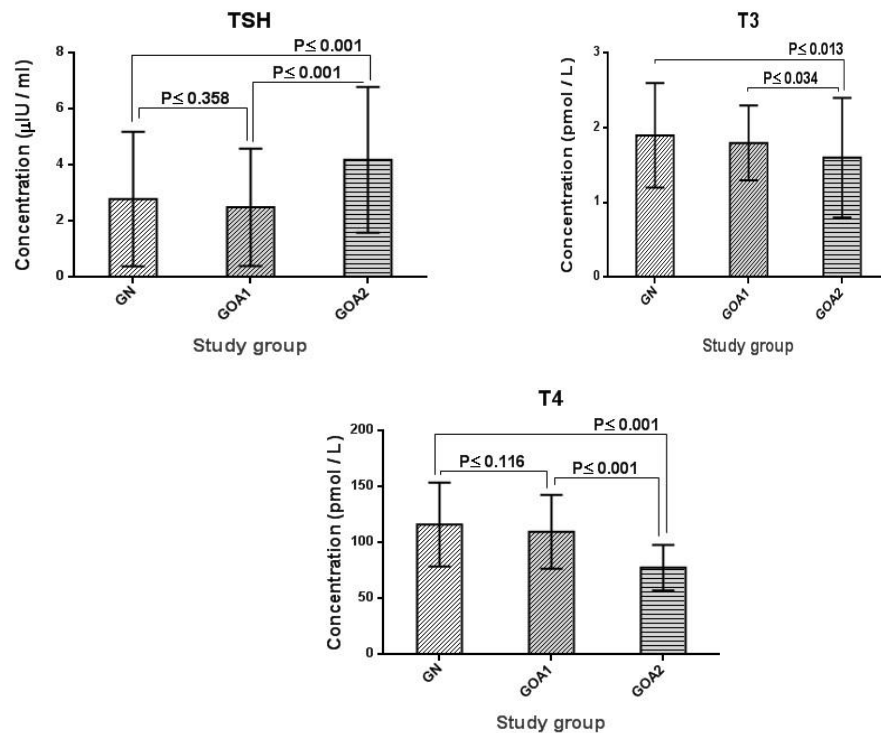Values of TSH, T3 and T4 of GOA 1 [2.5 ± 2.1, 1.8 ± 0.5 and 109.8 ± 33, respectively] were associated insignificantly (P□0.05) to values of these markers of GN [2.8 ± 2.4, 1.9 ± 0.7 and 116.4 ± 37.5, respectively]. Respectively, these markers confirmed a significant correlation (P<0.05) for values of the GOA 2 [4.2 ± 2.6, 1.6 ± 0.8 and 77.7 ± 20.4, respectively] and GN, as well as with the values of GOA 1 (Figure 9).

Figure 9. Findings of using walking aids among the GN, GOA 1 and GOA 2 study population.

The association of TSH to the severity of OA among the study population reported that there were significant differences (P<0.05) in their values at the crude as well as adjusted 1 and 2 models (Table 1).

TSH	Person without OA	Person with doubtful to minimal OA	Normal vs Doubtful to minimal OA	Person without OA	Person with Moderate to Severe OA	Normal vs Moderate to Severe OA	Person doubtful to minimal OA	Person with Moderate to Severe OA	Doubtful to minimal OA vs Moderate to Severe OA
Crude Model									
0.27 to 4.2 (Reference)	129	89	1	129	27	1	89	27	1
<0.27	7	8	1.65 (0.57 - 4.73)	7	5	3.41 (1.13 - 9.56)	8	5	2.06 (0.62 - 7.81)
>4.2	24	13	0.78 (0.37 - 1.62)	24	19	3.78 (1.92 -7.85)	13	19	3.61 (2.13 - 8.42)
Adjusted Model 1									
0.27 to 4.2 (Reference)	129	89	1	129	27		89	27	1
<0.27	7	8	1.71 (0.58 - 5.12)	7	5	3.11 (0.77 - 9.43)	8	5	2.25 (0.60 -7 .31)
>4.2	24	13	0.81 (0.38 - 1.71)	24	19	3.12 (1.77 - 8.24)	13	19	3.53 (1.76 - 8.17)
Adjusted Model 2									
0.27 to 4.2 (Reference)	129	89	1	129	27	1	89	27	1
<0.27	7	8	1.82 (0.59 - 5.56)	7	5	2.89 (0.69-9.21)	8	5	2.99 (0.76 - 9.89)
>4.2	24	13	0.82 (0.38 - 1.79)	24	19	2.74 (1.65 - 8.13)	13	19	2.87 (1.74 - 7.47)

Table 1. Association of TSH hormone to the severity of OA.

Discussion

Worldwide, the prevalence of OA in developed and developing countries has elevated significantly in the last decades due to increasing the factors of risk, which interact in a complex manner. Data from this study showed that weight and BMI factors potentially impact increasing the prevalence and severity of OA. However, the mechanism(s) for initiating and progressing OA remains poorly known, though the overweight runs high risks for OA[32, 33]. The relation of weight to OA has long been identified since obese patients developed the disease earlier and have variable and severe signs of illness, more significant risks of being infected and technically more obstacles to surgical replacement of a joint[34, 35].

Additionally, it has been thought that obesity participates relatively in systemic inflammations by adipokines secretion, which stimulates the catabolic process in articular chondrocytes, resulting in the degradation of extracellular matrix by up-regulation of matrix metalloproteinase[36, 37]. Several studies state that lifestyle changes can increase the identification of OA management and follow-up advice about the significance of elevated physical treatment and reducing weights [38-41]. Christensen et al. (2005) demonstrated that obese patients with knee OA can function normally by losing weight. For BMI, many reports have demonstrated a potential correlation between knee OA and BMI[42, 43], whereas others found a relationship between hip OA and BMI[44, 45]. However, Singer et al. (2018) detected significant contact between knee/hip OA and BMI, with an increase in BMI contributing significantly to an increase in OA46. Reyes et al. (2016) revealed the association between being overweight and clinically diagnosed hand, hip and knee OA[47].

For gender factor, though insignificant differences were shown between values of study groups (GN, GOA1 and GOA2) in both sexes, females showed a higher significant association with OA than males. These findings were similar to that found by many studies[48, 49], and in contrast with others [50, 51]. In females, a high incidence of OA might be attributed to genetic differences [52], immune changes and detrimental effects on intrinsic material properties of articular cartilage due to decreased concentration of estrogen at menopause time [49, 53]. Also, vitamin D in-

sufficiency due to malnutrition or lowered exposure to sunlight might increase the susceptibility of females to OA[54, 55].

Our findings demonstrated a significant association between OA and the demographic characteristics of the study population. This study showed that the level of education has a lowered risk of increasing OA, suggesting that occupational class, working conditions and physical activities play a role in the level of education and OA [56]. For the smoking factor, our findings were similar to many previous and recent studies that indicated no significant relationship between OA and smoking [51, 57, 58]. However, Hui et al. (2011) referred to the protective association between smoking and OA when BMI does not adjust, and smokers have fewer OA risks than non-smokers [59]. In this study, we showed that the arthritis factor had a significant relation to patients of severe OA (GOA2) only. Hunter et al. (2005) concluded that radial subluxation predisposes for subsequent trapeziometacarpal OA in men [60]; whereas, Rupasov et al. (2017) summarized that radiographic alterations in posttraumatic arthritis were typically reflected in underlying joint trauma resulting in symptoms of OA [61].

Our results indicated that there was a significant association between chronic and OA. The effect of chronic illness on health quality might be a reflex of differences in daily activities, particularly social, to result in OA or other joint diseases [62, 63].

For example, many researchers highlighted a great OA frequency in diabetic individuals due to the deleterious impact of excessive accumulation of glycation end-products and the development of systemic inflammations and oxidation stresses [64]. Further association of OA was detected in heart, kidney, liver and lung diseases [65-69].

We found that physical activity is associated with OA but with variable effects. Exercise represents the most discussed and controversial non-pharmacologic management strategy for OA since regulated low to moderate physical activities have preventing and therapeutic effects for OA patients. In contrast, type, duration and volume of intense and robust activity encompassed variable risk factors for symptomatic OA [70-72].

Different data in the current study was obtained for using walking aids and their association with OA. Many devices were used worldwide to aid OA patients, such as orthopedic footwear, brace, walkers, forearm crutches and walking stick [73]; however, information about the exact need for these aids is scarce. Additionally, many authors hypothesized that OA patients have a lowered risk of osteoporosis and, subsequently, fractures regarding the protective role of OA during the assessment of patients [74, 75]. Nonetheless, Arden et al. (2006) mentioned that elevated OA risks were not substantially decreased through adjusting of falls but attenuated the severity of falls sustained [76]. Other researchers recorded that the risk factors of falls in OA patients included increasing the number of symptomatic joints, comorbidities, muscle weakness, and impaired balance [77-79]. Manlapaz et al. (2019) referred to the low limited evidence for using walking aids and conflicted results that concerned using these devices in older patients [80].

In this study, normal and doubtful to minimal OA patients appeared to have an insignificant association with thyroid hormones (T3, T4 and TSH), while moderate to severe OA patients revealed a significant relation to these hormones. Thyroid hormones appear practical in remodeling and maintaining bones [81] with their importance for joints [82] and articular cartilage 83. Increasingly, the effect of deiodinase polymorphisms on OA has more worldwide interest because iodothyronine deiodinase represents a group of proteins that contributed to the local homeostasis of T3 and T4 [84, 85]. Shiroky et al. (1993) suggested that the frequency of thyroid dysfunction with OA might be associated with fatigue, anemia, arthritis and metabolic abnormalities [86]. Tagoe et al. (2012) recorded that hypothyroidism is related to OA and other forms of arthritis, with the existence of disease in indi-

viduals with a dysfunction in thyroid hormones, particularly autoimmune thyroid disease, increasingly recognized [87]. Li et al. (2019) mentioned the expected prevalence of thyroid dysfunction among OA patients [88]. Kim et al. (2020) concluded that both hyperthyroid and hypothyroid cases were related to musculoskeletal abnormalities and that examination of these abnormalities can be helpful in uncontrolled thyroid dysfunction [89]. GEZGİNASLAN et al. (2022) reported that thyroid function disorders might worsen OA symptoms [90].

Conclusion

Bodily and demographic risk factors showed variable findings concerning their association with OA. There is an increased risk of moderately to severe OA in patients with a thyroid dysfunction history. The potential role of thyroid hormone signaling in OA pathogenesis must be recognized. To date, less is known about the impact of thyroid hormones on muscle weakness and the impact of that weakness on the development and progression of OA. Furthermore, it seems timely to revisit the possible role of systemic hormones in the list of risk factors for OA.

Conflict of interest

There is no conflict to be interested.

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