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The Impact of Pharmaceutical Care Intervention on the Depressive Symptoms of Patients Diagnosed with Hypothyroidism

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Abstract

Pharmaceutical care interventions are a set of recommendations/interventions given by the pharmacist to improve therapeutic compliance, reduce complications, solve a drug therapy problem and improve patients' quality of life with chronic diseases by achieving patient satisfaction. The role of pharmaceutical care intervention in improving the condition of patients with hypothyroidism is still uncovered in Sulaimani city in Iraq, therefore, the current study aimed to evaluate the role of pharmaceutical care interventions in improving the outcome of depression in patients diagnosed with hypothyroidism. Fifty-eight patients were enrolled in the study and were randomly allocated into two groups: pharmaceutical care and the control group, both groups were interviewed by the pharmacist using a specific questionnaire. It is the fourth version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) for assessing their psychological state at the beginning and at the end of the study and data are recorded by the pharmacist. Blood samples were collected and utilized for analyzing the levels of thyroid function tests, lipid profile tests and blood glucose parameters at baseline and six weeks after. The pharmaceutical care group received all the education about their medications and how to minimize drug-related problems; improve the outcome and quality of life. Additionally, the pharmaceutical intervention included correcting some biochemical parameters. The study findings suggest that pharmaceutical care intervention and pharmacist's role over six-weeks period could improve the patient's depressive condition. In addition, it can improve some biochemical parameters and quality of life significantly.

Keywords: Hypothyroidism, DSM-IV, Pharmaceutical care intervention, Depression.

تأثير تدخل الرعاية الصيدلانية على أعراض الاكتئاب لدى مرضى قصور الغدة الدرقية

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الخلاصه

تدخلات الرعاية الصيدلانية هي مجموعة من التوصيات / التدخلات التي يقدمها الصيدلاني لتحسين الامتثال العلاجي وتقليل المضاعفات وحل المشاكل التي ترافق اخذ العلاج وتحسين نوعية حياة المرضى المصابين بالأمراض المزمنة من خلال تحقيق رضا المريض. دور تدخل الرعاية الصيدلانية في تحسين حالة المرضى الذين يعانون من قصور الغدة الدرقية لا يزال غير مكشوفاً في مدينة السليمانية في العراق ، لذلك هدفت الدراسة الحالية إلى تقييم دور تدخلات الرعاية الصيدلانية في تحسين نتائج الاضطرابات النفسية والاكتئاب لدى مرضى قصور الغدة الدرقية. تم تسجيل ٥٨ مريضًا في الدراسة الحاليه وتم تقسيمهم عشوائيًا إلى مجموعتين: المجموعة التي تتلقى الرعاية الصيدلانية ومجموعة المراقبة ، تمت مقابلة كلتا المجموعتين من قبل الصيدلي باستخدام استبيان محدد وهو الإصدار الرابع من الدليل التشخيصي والإحصائي للاضطرابات النفسية (DSM-IV) لتقييم حالتهم النفسية في بداية الدراسة ونهايتها وتم تسجيل البيانات بواسطة الصيدلاني. تم جمع عينات الدم واستخدامها لتحليل مستويات اختبارات وظائف الغدة الدرقية ، واختبارات مستوى الدهون ، ونسبة هيموغلوبين A_{1c} وسكر الدم العشوائي عند بداية الدراسة وبعد ستة أسابيع. تلقت مجموعة الرعاية الصيدلانية جميع التثقيف حول أدويتهم وكيفية تقليل المشاكل المتعلقة بالأدوية ؛ تحسين نتائج ونوعية الحياة. بالإضافة إلى ذلك ، وقد كان للتدخل الصيدلاني دور في تصحيح بعض المتغيرات البيوكيميائية.

الكلمات المفتاحية: قصور الغدة الدرقية ، الدليل التشخيصي والإحصائي للاضطرابات النفسية ، تدخل الرعاية الصيدلانية ،الاكتئاب.

Introduction

Depression, is one of the most prevalent chronically debilitating conditions that can lead to low quality of life [(1)]. Meanwhile, the thyroid hormones (triiodothyronine (T3) and thyroxine (T4) which are abundantly distributed throughout the central nervous system, controlling the development of neurons and forming synapses between them [(2)]. Proposing that alterations in the hypothalamic-pituitary-thyroid (HPT) axis have been linked to depression [(3)], according to studies, depression and other psychological issues are positively correlated with hypothyroidism [(4)].

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Hypothyroidism, is a chronic disease associated with a deficiency in the thyroid hormones [5]. Development of thyroid insufficiency in adulthood is associated with reduced basal metabolic rate, poor resistance to cold, weight gain, weariness, muscle weakness, lethargy, malaise, hypercholesterolemia, and unpleasant mental states such as diminished cognition and depression [6]. The population in undeveloped parts of the world acquire hypothyroidism due to inadequate iodine in their diet. Therefore, many countries aim to boost iodine consumption by adding iodine to salt, while in other areas of the world where people ingest enough iodine, the most common cause of hypothyroidism is Hashimoto's disease, it is an autoimmune disease in which the immune system attacks the thyroid gland by producing cells and antibodies [7].

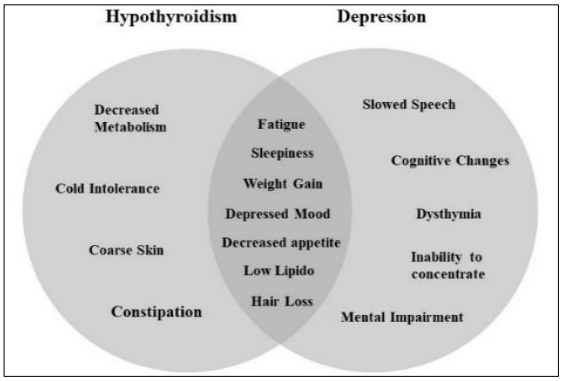

Figure 1. Theoretical escalation of frequent symptoms of depression according to the degree of hypothyroidism. As the disease progresses, the depressive symptomatology worsens. [18].

Nowadays, individuals with hypothyroidism are recommended to be initiated with levothyroxine replacement therapy only when their Thyroid stimulating hormone (TSH) level is above 10 mIU/L [8] or if they are trying to be pregnant, have thyroid autoimmunity or cardiovascular risk factors, including high blood pressure and high cholesterol [9]. However, there is a lack of enough credible evidence that support the use of levothyroxine replacement therapy to produce positive changes in mental health outcomes [10]. Therefore, the current research was performed to improve the depression state outcome of patients with hypothyroidism by pharmaceutical care interventions in conjunction with levothyroxine. Levothyroxine is the mainstay of treatment for hypothyroidism, it has been considered to be the ''Gold Standard'' for the treatment of primary hypothyroidism for more than 60 years [11]. Upon diagnosis of hypothyroidism, lifelong treatment with levothyroxine is often initiated, except in cases when hypothyroidism is caused by temporary types of thyroiditis or medications that can be discontinued [9.12]. The initial dose of levothyroxine is determined by the patient's age, the presence of co-existing heart illness, aetiology and severity of hypothyroidism. The levothyroxine dose is titrated until reaching the goal where TSH levels are normalized at between 0.4 and 4.0 mIU/L [13]. The concept of pharmaceutical care, is a process of pharmacist collaboration with the patient and other health professionals to develop, implement, and monitor a therapeutic plan to generate a particular therapeutic outcome for the patient [14]. During the process of pharmaceutical care, the pharmacist ought to assess the patient's medical issues and medications that contribute to the detection of drug-related problems (DRPs), develop a care plan, follow up with the patients and perform an intervention to solve DRPs [15]. The role of the pharmacist has significantly improved the quality of life for patients who were suffering from chronic kidney disease. This was adopted in a research in Iraq – Sulimaniyah in 2020 [16].A link between hypothyroidism and depression has been estimated for many years. However, the exact nature of the link has been difficult to identify because the methods used to measure psychological impairment vary between studies, which may affect their comparability. This is because of making psychological diagnoses in a study with thousands of participants is challenging as well as some symptoms of hypothyroidism and depression overlap as shown in Figure 1. Some studies have looked at real diagnoses of 'depressive disorders, which are mainly obtained from database records (depression admissions or appointments) or self-reported former or present depression diagnoses. Other researchers have employed validated questionnaires to detect depression symptoms, and their validated results were positively accepted [17]. It should be noted that enrolling in pharmacological care may help people with hypothyroidism experience fewer symptoms of psychological disorders. Meanwhile, Selenium; is a rare element that can be found in soil and some foods like whole grains, Brazil nuts, sunflower seeds, and seafood [19]. Although selenium is not produced by the body, it is essential for the proper thyroid and immune system function [20]. Furthermore, it has a wide range of pleiotropic effects, including anti-oxidant and anti-inflammatory properties as well as the synthesis of active thyroid hormone [21]. Selenium has been used as an alternative medicine to treat, to prevent and to help patients with Hashimoto's thyroiditis and high cholesterol [22]. Several studies have shown that selenium supplementation reduces thyroid peroxidase levels (TPO) as well as the severity of hypothyroidism symptoms [23]. Prospective studies have typically demonstrated that increased selenium levels reduce the risk of lung [24], prostate [25], colorectal [26], and bladder cancers [27], but trial results have been inconsistent, highlighting the fact that selenium supplements are only beneficial if

nutritional intake is insufficient [28]. Patients with hypothyroidism are more anxious and depressed than euthyroid controls [8]. However, depressed mood and cognitive changes predominate, including inattentiveness, inability to concentrate, slower speech, and fatigue which appear to be the common denominator for hypothyroidism and depression [18]. As hypothyroidism intensifies, more symptoms are likely to appear, indicating an association between the entity of thyroid failure and neuropsychiatric disorders [29]. This study aims to implement the role of pharmaceutical care intervention with the use of 200µg selenium supplements on patients diagnosed with hypothyroidism. Moreover, the objective of such implementation is to improve the depressive symptoms and patients' quality of life.

Methodology

Study design

The present study was performed in the Department of Clinical Pharmacy, College of Pharmacy at the University of Sulaimani in collaboration with High Quality Hospitals/ Anwar Sheikha Medical City/ Outpatient Clinics Department in Sulaimani city/Kurdistan Region of Iraq through the period of January 2022 until June 2022. Figure 2 shows the study design of this research. This prospective, observational, pilot study included 60 patients with hypothyroidism that have been diagnosed and treated previously by internists and endocrinologists. The participants are randomly assigned into two groups; Group I patients, the control group, consisted of 30 patients (9 Males and 21 females) with a mean age of (39.4 ± 11.1) years, who received only levothyroxine according to their physician recommendations and were followed up without any intervention. Group II, a pharmaceutical care intervention group, consisted at first of 30 patients, but during the process of the intervention, 2 patients were lost to be follow up. Therefore, a total of 28 patients (8 Males and 20 females) were included in the interventional group and had a mean age (39.11 ± 14.6) years, received pharmaceutical care intervention and 200µg selenium supplementation per day (only for patients with low blood selenium level). In addition, to their levothyroxine treatment.

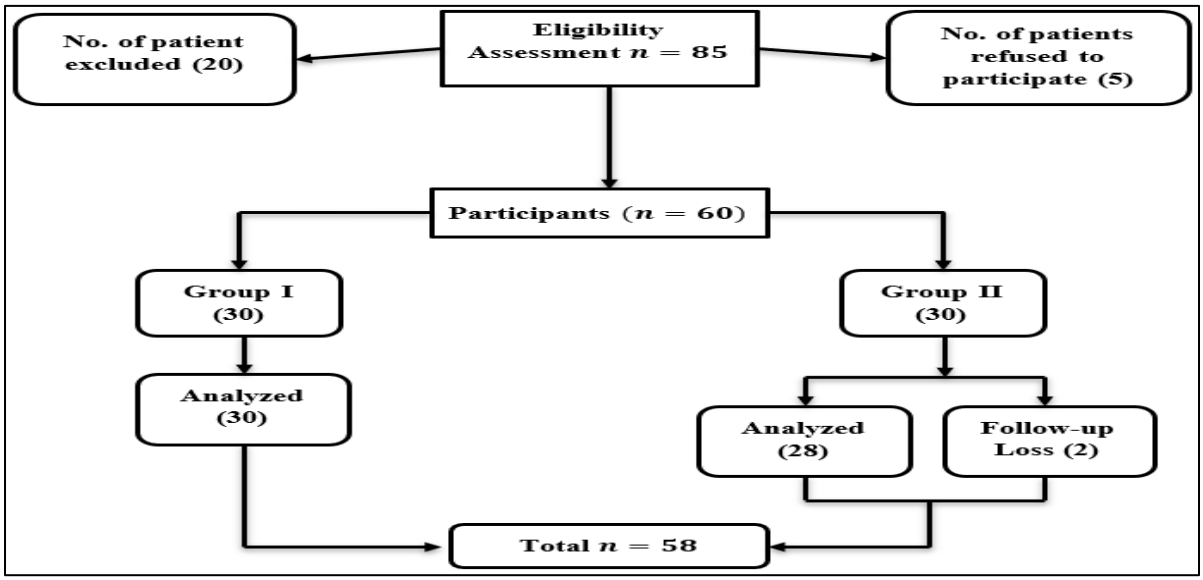

Figure 2. Flowchart displaying the participant sampling process

Inclusion and exclusion criteria

In this study, both genders were included and were aged 18-70 years old. The participants were diagnosed with hypothyroidism based on serum thyroid-stimulating hormone (TSH) measurement and were on levothyroxine.

Meanwhile, due to the following reasons patients were excluded from the study:

1. History of toxic nodular goiter, grave's disease, postpartum thyroiditis, cardiovascular disease (CVD).
2. Diabetic patients who were receiving metformin.
3. Previous radioactive iodine therapy.
4. Poor compliance to the medication.
5. Previous thyroidectomy or any surgery related to the thyroid.
6. Co-administration of drugs known to affect thyroid function e.g., lithium and amiodarone.
7. Allergy to selenium or levothyroxine.
8. Pregnant and lactating women or the ones who were planning for pregnancy.

Pharmaceutical care intervention process

The two interventional sets that were used in this research were; pharmaceutical care intervention which is the pharmacist's plan of action to increase patient compliance, reduce complications, solve drug therapy problems, and improve the quality of life of patients with chronic diseases, and the co-administrating of 200µg selenium supplementations/day (Nature's Bounty co. the USA) in individuals who were selenium deficient, Laboratory assessment and a

psychological evaluation of the patients were done at the beginning of the study and after six weeks of the study.

The pharmaceutical care intervention that was performed by the pharmacist included the following:

1. Gathering the data required to comprehend the patient and their pharmaceutical experience.
2. Ascertaining if medications are appropriate, effective and safe for the patient and checking if the patients are adherent to their medications (compliance).
3. Find out drug-related problems and solve them (e.g. drug-drug interaction),
4. Providing the patients with the appropriate diet and what should not be consumed to improve their thyroid function.
5. Providing the patients with selenium supplements (200µg/day) according to their body level of selenium.
6. following up with the patients regularly (by visits, texting or direct phone calls).
7. documenting any changes in their condition and medications and describing the desired therapeutic goals.

Evaluation of the psychological state of the patients

The Diagnostic and Statistical Manual of Mental Disorders questionnaire [30] was used to assess patients' psychological state and their likelihood of developing mental abnormalities before and after the intervention. According to DSM-IV, major depression disorder represents the classic condition of depressive disorders. It is characterized by discrete episodes of at least 2 weeks' duration (although most episodes last considerably longer) involving clear-cut changes in affect, cognition, neuro-vegetative functions and inter-episode remissions. A diagnosis based on a single episode is possible, although the disorder can reoccur in most of the cases [31]. Patients were considered to have major depression if they had a history of at least five of the symptoms listed below. Furthermore, patients who presented with at least 3 of the depressive symptoms during the same two-week period or more, at least of which is either depressed mood or loss of interest were considered to have minor depression. Insomnia, suicidal ideas and suicidal attempts were also considered separately. The depressive symptoms that were considered in this study include the following:

1. Depressed mood most of the day
2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day
3. Significant weight loss when not dieting or weight gain or decrease or increase in appetite nearly every day
4. Insomnia or hypersomnia nearly every day.
5. Psychomotor agitation or retardation nearly every day
6. Fatigue or loss of energy nearly every day.
7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day
8. Diminished ability to think or concentrate, or indecisiveness, nearly every day.
9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

The criterion symptoms for major depressive disorder must be present nearly every day to be considered present, except for weight change and suicidal ideation. A depressed mood must be present for most of the day or nearly every day.

Biochemical assessment

The anthropometric measures such as body weight (kg), height (m), and waist circumference (cm) were measured using a sensitive electronic balance, standard stadiometer, and a steel tape of measurement, respectively. Body mass index (BMI) was calculated as:

$$\text{BMI } (\text{kg/m}^2) = \text{body weight (kg)}/[\text{height (m)}]^2 \quad (32)$$

For laboratory tests measurement, 10 mL of venous blood was drawn from each patient and centrifuged at 3,800 r.p.m for ten minutes at test tubes free of anticoagulants for separation of the serum and were stored in a 1.5ml Eppendorf tube -80 °C to be used for determination of thyroid function tests (TSH, T3 and T4), low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglyceride levels (TG), cholesterol, HbA_{1c}, blood glucose and selenium level (only measured once at the beginning of the study to determine which patient had low selenium levels for the purpose of providing them with selenium supplementations) using a Cobas-311 auto-analyzer according to the instruction of the manufacturer.

Statistical analysis

The results were expressed as mean ± standard deviation SD. The continuous variables of the two groups were compared using a two tailed one-way analysis of variance (ANOVA) while categorical variables were analyzed using Chi-square test. A P-value of <0.05 is considered statistically significant. For analyzing data, the software StataCorp LP was used.

Results

Baseline characteristics

Sixty eligible patients consented to participate in the research. A total of 58 patients completed the analysis to fulfill the study objectives. Those were included in the data analysis, 30 patients were included in the control group, and 28 patients were included in the interventional group. There were no significant differences between both groups regarding age, gender, BMI, educational status,

smoking and alcohol drinking history, and family history.

Table (1) shows the baseline characteristics of the participants who were included in this study. The first column illustrates the baseline demographic characteristics that were considered in the study. The second column shows the percentages and mean ± SD of the control group, while the third column manifests the percentages and mean± SD of the intervention group baseline characteristics. The forth column shows the P-values that were considered to be significant when P<0.05. The mean age of the participants in the interventional group was (39.1 ± 14.64) and (39.4 ± 11.1) in the control group and the average BMI was (26.30 ± 5.42) and (26.97 ± 4.65) (kg/m^2) for the interventional group and control group respectively. Regarding the educational level, most of the patients 11 (39%) in the interventional group were primary (finished primary school only), while most of the patients 13 (44%) in the control group were owning a high educational level. Most of the patients, 16 (57%) in the interventional group, and 22 (73%) in the control group had a family history of thyroid dysfunction, especially hypothyroidism.

Hypertension was the most common comorbidity in both groups where 5 (17 %) of the interventional group and 6 (20%) of the control group were suffering from this comorbidity. There was only a significant difference in the participant's residency with a value of (0.038).

Table 1. Baseline characteristics of the study participants

Baseline Characteristics	Control group (n =30)	Intervention group (n =28)	
	n (%) /mean ± SD	n (%) /mean ± SD	P-value
Gender			
Male (%)	9 (30)	8 (29)	0.905
Female (%)	21 (70)	20 (71)	
Age (Years)	39.4 ± 11.1	39.1 ± 14.64	0.932
Residency:			
Rural (%)	3 (10)	9 (32)	0.038*
Urban (%)	27 (90)	19 (68)	
Smoking:			
Yes (%)	6 (20)	4 (14)	0.565
No (%)	24 (80)	24 (86)	
Alcoholic:			
Yes (%)	2 (6.7)	2 (7.1)	0.934
No (%)	28 (93.3)	26 (92.9)	
Level of education:			
Preprimary (%)	1 (3.3)	0 (0)	0.050
Primary (%)	3 (10)	11 (39.3)	
Lower secondary (%)	6 (20)	7 (25)	
Upper secondary (%)	7 (23.3)	5 (17.8)	
Post-secondary (%)	13 (44.3)	5 (17.8)	
Family history of thyroid dysfunction:			
Positive (%)	22 (73.3)	16 (57.1)	0.195
Negative (%)	8 (26.7)	12 (42.9)	
Concomitant Illnesses			
Diabetes Mellitus (%)	1 (3.3)	4 (14.3)	-
Hypertension (%)	6 (20)	5 (17.8)	
Others (%)	6 (20)	5 (17.8)	
No concomitant disease besides hypothyroidism (%)	18 (60)	18 (64.3)	
Anthropometric Measurements			
Weight (Kg)	78.77 ± 13.15	73.67 ± 14.45	0.168
Height (Cm)	171.03 ± 6.65	167.67 ± 10.2	0.149
Waist Circumference (Cm)	97.63 ± 17.69	100.78 ± 16.9	0.491
BMI (Kg/m^2)	26.97 ± 4.65	26.30 ± 5.42	0.612

Data are presented as a percentage or mean ± SD: n: number of patients, Chi-square and unpaired t-test were utilized to predict significance at P<0.05. *Symbol denotes significant difference.

The effects of pharmaceutical care on depression

Table (2) shows the effect of pharmaceutical care intervention on participants during of intervention and follow-up that lasted for six weeks. The depression state of the interventional group was improved after the due period. However, the improvement of the depressive condition was not significant as is seen from the p-value of ($P<0.05$). Most of the patients 13 (46.4%) in the interventional group were suffering from major depression and 10 (35.7%) were complaining of having major depression after the due period of intervention and follow-up. In addition, only 2 patients (7.1%) were presented with minor depression at the beginning of the process, and 5 patients (17.8%) were represented with symptoms of minor depression at the end of the process. On the other hand, 13 (46.4%) were psychologically normal and had no depressive symptoms across the study period.

The table also shows a sensible increase in the depressive symptoms of the patients in the control group with around ($P<0.05$). Before the follow-up process, 11 (36.7%) and 5 (16.7%) were presented with major depression and minor depression respectively, after the follow-up process, 15 (50%) of patients were complaining of having major depression and only 1 (3.3%) were considered to have minor depression, the rest of the patients 14 (46.7%) had no depressive symptoms and were psychologically normal before and after the follow-up process. Isolated insomnia and suicidal ideation were considered separately.

Table 2. Compares the baseline and the outcomes data of depressive symptoms between the two groups.

Psychological Symptoms	Control Group		P-value	Intervention Group		P-value
	Baseline	After six weeks		Baseline	After six weeks	
Depression						
Major Depression	11 (36.7%)	15 (50%)	0.272	13 (46.4%)	10 (35.7%)	0.664
Minor Depression	5 (16.7%)	1 (3.3%)	0.070	2 (7.1%)	5 (17.8%)	0.225
No Depression	14 (46.7%)	14 (46.7%)	-	13 (46.4%)	13 (46.4%)	-
Other symptoms						
Isolated Insomnia	1 (3.3%)	0 (0.0%)	0.296	0 (0.0%)	1 (3.3%)	0.313
Suicidal Idea	7 (23.3%)	9 (30%)	0.905	9 (32.1%)	8 (28.6%)	0.771

The results are expressed as numbers (%). P-value was calculated using the chi-square test for comparing the baseline and after of both groups.

The effects of pharmaceutical care on biochemical parameters

As it can be seen from Table (3) the baseline data and the outcome of pharmaceutical care intervention on variable biochemical parameters across six weeks.

A statistical analysis was performed using one-way anova test to compare between the two groups which is expressed as F-value in the table. The analysis showed a significant change in the levels of LDL and RBS during the period of the study with values of 0.019 and 0.034 respectively. The levels of T3 and T4 were reduced generally. However, the levels of TSH of the control group was elevated after six weeks. Furthermore, the analysis showed an increase in the levels of HDL for both groups. Simultaneously, the levels of triglycerides and cholesterol were elevated in the control group and reduced in the intervention group but the change was not significant.

A two tailed paired t-test was used to compare the baseline values with the values that were measured after six weeks for each group individually. The comparison within the groups showed some significant results for both groups. The control group had a significant increase in the levels of LDL and cholesterol following six weeks of follow up with a P-values of 0.001 and 0.030 respectively. In addition, the levels of TSH, HDL, TG and RBS were all elevated but not in a significant manner. Nonetheless, the levels of T4 were slightly decreased during the process of follow up. However, pharmaceutical care intervention showed a significant decrease in the levels of T3 with a probability value of 0.042 and a remarkable decrease in the levels of triglycerides was noticed with a p-value of 0.015.

Table 3. The effects of pharmaceutical care intervention on biochemical parameters of patients with hypothyroidism across a duration of six weeks.

Parameters	Control Group		Intervention Group		F-Value	P[1]	P[2]
	Baseline	After Six Weeks	Baseline	After six Weeks			
TSH (uIU/ml)	5.43±2.99	5.65±2.17	4.40±1.62	4.35±1.28	0.060	0.216	0.571
T3 (nmol/L)	1.62±0.59	1.59±0.52	1.51±0.26	1.46±0.25	0.520	0.211	0.042*
T4 (nmol/L)	101.01±22.47	100.89±21.59	94.97±17.88	93.14±16.19	0.304	0.899	0.070
HDL (mg/dL)	55.42±15.43	55.68±14.90	51.51±13.17	52.51±11.20	0.577	0.624	0.289
LDL (mg/dL)	105.00±28.15	109.21±28.17	121.42±20.80	122.07±21.55	0.019*	0.001**	0.691
Triglycerides (mg/dL)	155.91±46.55	159.21±46.40	141.57±51.55	138.50±48.77	0.309	0.087	0.015*
Cholesterol (mg/dL)	164.07±54.76	172.17±47.43	185.11±32.91	183.90±30.38	0.196	0.030*	0.471
RBS (mg/dL)	112.61±18.72	114.11±15.06	106.63±13.52	102.94±16.67	0.034*	0.564	0.293
HbA_{1c} (%)	5.23±0.77		5.69±0.87		0.062		

Results are presented as Mean ± SE (95% confidence intervals). P-value was calculated by two tailed one-way analysis of variance to demonstrate changes in the levels of parameters, and a two tailed paired t-test to compare the changes in the parameter levels across a duration of six weeks. * Symbol denotes significant difference, ** Symbol denotes highly significant difference.P^1: Denotes the significant within the control group. P^2: Denotes the significant within the intervention group.

Pharmaceutical care intervention had caused a slight increase in the levels of HDL but the change was not significant with a P-value of 0.289. In addition, general decrease in the other parameters of lipid profile was noticed. Moreover, the baseline level of HbA_{1c} for both groups was varied, but the difference was insignificant with a value of 0.062.

Discussion

Thyroid Depression is one of the most symptoms of hypothyroidism and is found in association with thyroid dysfunction [33]. Basically, this study is the first study that introduced pharmaceutical care intervention to patients with hypothyroidism in Sulimaniyah city –Iraq. The objective was to investigate the effect of pharmaceutical care intervention and the role of clinical pharmacist in improving the depressive symptoms and biochemical parameters in patients diagnosed with hypothyroidism. According to the findings of this process, pharmaceutical care intervention and the contribution of the clinical pharmacist was effective in enhancing the outcomes of patients with hypothyroidism by decreasing their depressive symptoms, solving DRPs, recommending proper diet and educating the patients about their medications and the impact of good compliance to achieve the desired therapeutic outcomes. The participants had similar values at the baseline, yet significant variations were observed regarding their residency with a value of (0.038) where the number of the urban patients in the control group was higher than that of the intervention group. Most of the included participants were females as it is known that hypothyroidism is more common in women than men as reported by Zhao [34]. This is probably because of the pituitary losses its normal function as the female age which could result in improper thyroid function as well as the thyroid gland can increase in size during pregnancy and lead to consequences of thyroid dysfunction especially in iodine-deficient women. In addition, most of the included females' patients in the study were married and had children. From the obtained results, the majority of patients 37 (64%) had a positive family history of thyroid dysfunction, which could be due to an interaction between genetic predisposition and environmental triggers that lead to progress of hypothyroidism.

Regarding the depressive condition, at the baseline, major depression was more common in the intervention group patients 13 (46.4%) than the control group 11 (36.7%), the reason might be due to their poor knowledge about their medications and the consequences of their condition that might occur when they're not treated probably or the poor compliance to their medications especially levothyroxine. Therefore, the intervention group have received full guidelines and instruction about the effect of their medications, the most highlighted instruction was to take levothyroxine 30 minutes before meal to ensure full absorption as most of the patients were taking it directly before meal.

Subsequently, minor depression was more common in the control group patients 5 (16.7%) than the intervention group patients 2 (7.1%), the rest of the patients were psychologically normal and had no depressive symptoms at the baseline and after six weeks equaling to 14 (46.7%) and 13 (46.4%) patients in the control group and intervention group respectively. Furthermore, only one patient (3.3%) was presented with isolated insomnia in the control group and non were presented in the intervention group, while 7 (23.3%) and 9 (32.1%) of the patients had suicidal ideations in the control group and intervention group sequentially. These findings support the meta-analysis by Tang et al [35] which demonstrated that hypothyroidism was positively associated with the risk of depression. Contentedly, the results were satisfactory after applying the process of pharmaceutical care intervention and the contribution of the clinical pharmacist where the patients received full instructions and guidelines about their conditions, medications and proper diet, following the baseline with six weeks, major depression symptoms were more common in the control group than the intervention group with percentages of (50% and 35.7%) respectively. The change was not significant presumably due to the small sample size of the participants (n=58), short duration of intervention and follow up (six weeks) and the poor knowledge and conviction about the effects of pharmaceutical care intervention. However, the data had showed that the contribution of the clinical pharmacist can have a positive impact in improving the depression outcome of patients with hypothyroidism in a short duration. After six weeks of intervention and follow up, the ratio of the patients who presented with minor depression was higher in the intervention group compared to the control group, this is probably because some patients had major depression on the baseline and were improving due to the intervention but were still suffering from some depressive symptoms in the frame of minor depression. Moreover, after the proposed period of intervention, the number of patients with suicidal attempts and ideations was higher in the control group compared to the intervention group with ratios of (30% and 28.6) sequentially, supporting the positive impact of pharmaceutical care intervention in consistent with Jeong [36] meta-analysis.

Concerning the effect of pharmaceutical care intervention on thyroid function tests, glycemic control and lipid profile. Generally, a notable change had occurred in the patients' parameters after receiving pharmaceutical care intervention. The influence of the intervention and the administration of selenium supplements (200µg/day) was marked on the thyroid function tests and mostly on the level of T3 which was reduced after six weeks of follow up in both groups but significantly in the intervention group, this is probably due to some reduction of levothyroxine doses of the control group that was performed by the physician across six weeks. Moreover, the intervention had a slightly positive result in lowering the levels of TSH in the intervention group with a value of (0.571) in contrast with the control group who had notable rising in the level of TSH with a P-value of (0.216) corresponding to Kobayashi et al [37] analysis. These values difference could be due to the contribution of the pharmaceutical intervention and selenium supplements which have the ability to reduce the levels of thyroid peroxidase antibody titer via reducing oxidative stress and eventually leading to reduction in the levels of TSH. On the other hand, the levels of T4 were declined in both groups and mostly in the intervention group but the change was not significant.

The lipid profile parameters in both groups had shown an elevation in the levels of HDL after six weeks of intervention and follow up, but none of them showed a significant change, this is probably due to the short period of intervention and the small sample size, although selenium supplements can elevate the levels of HDL according to Laclaustra et al [38]. The study revealed a sharp increase in the levels of LDL and cholesterol of the control group which could be due to the demographic characteristics of the population and their daily consumption of large quantities of fatty food. Simultaneously, the increase in the levels of cholesterol and LDL was insignificant in the intervention group, probably owing to the education that they have received about the hazards of fats on their health state and were recommended to reduce their daily fat intake which contributed to positive result comparing to that of the control group, another reason that assisted in these results was the selenium that had shown to reduce the levels of cholesterol and triglycerides respectively as reported by Rees et al [39]. Therefore, the intervention group had a significant reduction in the levels of triglycerides with a value of (0.015) only after six weeks while the control group had a sharp increase in cholesterol levels and slight elevation in triglycerides levels with a probability value of (0.03 and 0.08) respectively.

Finally, the study also highlighted the pharmaceutical care intervention role in improving the glycemic control in patients with hypothyroidism. The difference in the baseline values for both groups in regard to their RBS and HbA_{1c} level was insignificant. However, the control group showed an increase in their fasting glucose levels with a P-value of (0.564) in contrast to the intervention group which showed a notable decline with a probability value of (0.293). These data address the beneficial effects of pharmaceutical care intervention, patient education on the blood glucose levels and the ability of selenium to reduce the levels

of glucose in accordant with Alizadeh et al [40] analysis which aided in achieving satisfying results.

Conclusion

In conclusion, the current study demonstrated that depression is probably associated with hypothyroidism, addressing the necessities for clinicians to pay special attention to depressive symptoms in patients with hypothyroidism. Short-duration pharmaceutical care intervention can ameliorate depression in patients diagnosed with hypothyroidism. Moreover, pharmaceutical care intervention in conjunction with selenium supplementations can have a notable effect on variable biochemical parameters especially lipid profile and glycemic control only during six-weeks interval. Therefore, it is recommended to apply the pharmaceutical care intervention for a long-term duration to establish its effect on the depressive symptoms and more biochemical parameters in patients with hypothyroidism.

Recommendations for Future Works

The current study was conducted on limited number of participants for short-term therefore, for future works, it is recommended to determine the effects of pharmaceutical care intervention on larger population and for long-term. Furthermore, the evaluation of the effects of pharmaceutical care interventions in addition to selenium supplementation on additional selenium-dependent antioxidant enzymes such as thioredoxin reductase and additional parameters, as well as other antioxidant/oxidant analyses, are recommended to be done in future studies.

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Declaration of Interest

The authors declare no conflict of interests.

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Ethics Statements

This study was registered with the registration number (PH50-22) and obtained ethical approval from the Ethical and Scientific Committees at the University of Sulaimani, college of pharmacy before starting the recruitment of participants. Additionally, the patients signed an informed consent form and acknowledged that they had the right to refuse participation or withdraw from the study whenever they wanted to do so.

Author Contribution

Rafal Malik Kamil collected the data (patients) from Dler Shamsulddin Hamid's Clinic, wrote the manuscript and performed the analytical methods. Vian Ahmed Wasta Esmail developed the idea of the research. All authors discussed the results and contributed to the final manuscript.

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