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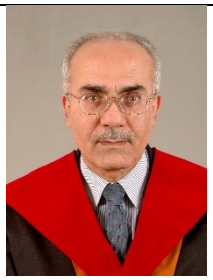	Prof Dr. Walaa Majid Amin Email: wami@ju.edu.jo	Member
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In Vivo Effect of Calcitonin Hormone on Rat Embryonic Dental Tissue (Histological, Biochemical, And Radiographical Studies)

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Abstract

Background: Calcitonin is a hypocalcemic factor secreted by the parafollicular cells of the mammalian thyroid and it plays a role in the calcification of the dental matrix.

Aim of the study: To evaluate the role of Calcitonin in the dental tissue

Material and Method: Sixty albino wister female rats (2-3 months of age, 200-250 gm of weight), were used in the present experiment. The rats were divided into:

1. The control group consists of 20 rats that received distilled water (I.M.).
2. Experimental group: consists of 40 rats, 20 rats received Calcitonin in 0.1 IU and remain 20 rats received 0.5 IU of Calcitonin (I.M).

From all pregnant rats, prenatal embryos (16 days I.U.L and 18 days I.U.L and postnatal embryos (1 day and 10 days old were studied radiographically using Promax X-ray and histologically (by Hematoxylin and eosin stain), biochemical analysis for alkaline phosphatase was done to blood sample obtained from prenatal group and delivery rats.

Results: The present study showed that embryos with Calcitonin 0.1 IU illustrate histologically:

a. Tooth germ in cap stage of 16 days of I.U.L.
b. Tooth germ in bell stage with cervical loop development at 18 days of I.U.L.
c. Tooth germ showed deposition of hard tissue enamel and dentin at one day old rat.
d. Tooth germ showed maturation of hard tissue enamel and dentin at 10 days old rat.

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Histologically: Embryos with 0.5 IU illustrate retardation in tooth development and impairment in calcification and maturation of enamel and dentin, with a wide zone of predentin formation. Radiographically: Cephalic and lateral views of embryos treated with 0.1 and 0.5 IU showed low density of skeletal bone and head. Biochemically: The mean concentration of alkaline phosphatase enzyme was recorded to be less in experimental groups (0.1 and 0.5 IU of calcitonin) in comparison to the control group and they are less in the 0.5 IU group in comparison to 0.1 IU group.

Conclusion: Calcitonin hormone of 0.1 IU dose showed to be the initiator and illustrates premature tooth development. Whereas 0.5 IU dose showed to be retarder for tooth germ development and effects on mineralization and maturation of bone and dental hard tissue.

Keywords: calcitonin, osteoclast, alkaline phosphatase

Introduction

Calcitonin is a hormone that received its name because of its secretion in response to induced hypocalcemia and hypocalcemia effect [1] therefore Calcitonin is known to participate in calcium and phosphorous metabolism in mammals. The major source of calcitonin from the parafollicular or C cells in the thyroid gland [2]

Calcitonin is an inhibitor of bone resorption, whose function is to prevent bone loss at times of stress on calcium conservation. This includes pregnancy, lactation, and growth [3]

Many studies have examined the effects of calcitonin on alkaline phosphatase enzymes and suggested changes in effect on bone development [4]

Other researchers studied the in vitro effects of calcitonin in the cultured tooth germ and its influence on the differentiation of odontoblast and the formation of hard tissue predentin and dentin [5,6].

Others studied the role of calcitonin in the calcification of dental matrix in vivo (rats) with chronic calcitonin deficiency only [7]

As incisor teeth of rats grow continuously and represent the rapidly growing calcified structure, and as there are no studies concerning the role of calcitonin dose in developing tooth germ, the present study was designed to investigate its effect [8].

Materials and Methods

Sixty Albino Wister female rats (2-3 months of age, 200-250 gm of weight), were used in the present experiment. Those rats were divided into two groups:

1. Control group: consist of 20 rats that received distilled water as an intramuscular injection (I.M).
2. Experimental group: consisting of 40 rats, 20 rats received Calcitonin in a concentration of 0.1 IU/ml, and the remaining 20 rats received 0.5 IU/ml as intramuscular injection.

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From all pregnant rats of both (experimental and control), groups of rats were sub-divided according to period of gestation life into:

1. Prenatal rat group includes: 16 days I.U.L. (41 embryos), and 18 days I.U.L. (42 embryos)
2. Postnatal rat group include One day old rats (15 rats) and 10 days old rat (15 rats).

Blood samples were obtained (before the scarifying date) from pregnant rats for the prenatal group and from delivery rats for the post-natal group for biochemical analysis. The prenatal group (16 days and 18 days of gestation I.U.L) and the post-natal group (1-day and 10-day old rat) were examined radiographically and histochemically.

Calcitonin Hormone: Miacalcin (Calcitonin - salmon) of 100 I.U/ml administered by intramuscular injection. It was injected in a dose of 0.1 and 0.5 I. U (80 and 200 mg/kg. B.W. alternatively) given by (1 ml) disposable sterilized syringe.

Distilled Water: The distilled water was injected into the control group in the same way as in the experimental group

Calcitonin Injections to Pregnant Rats: Sixty female Albino Wister rats with an age range of 2-3 months were first isolated from the rest, for two weeks to exclude any previous pregnancy. After examination and confirmation of non-pregnancy by the resident veterinary doctor, each female was paired with a male in separate cages which were checked daily for the presence of a vaginal plug. By calcitonin, the evidence of mating in the following morning was designated as day zero of gestation. Intramuscular injections were started on zero days of gestation daily for one week. Control females were injected by distilled water and the experimental ones injected

Histological Evaluation: After the experiment animals were scarified using ether vapour. The embryos from the uterus of the pregnant rats were obtained, separated the head from the body, and cut sagitally into two halves, and the specimens (concerning the incisors tooth only) were preserved in 10% buffered formalin for 72 hours for the histological process.

Histological Process:

Dehydration of specimens in a series of alcohol concentrations 40%, 60%, 80%, 95%, and absolute alcohol. Specimens were passed through two changes of xylol (xylene) for 15 minutes to get rid of any excess ethanol. Embedding of specimens in paraffin blocks. Serial sections of 5-micrometer thickness were obtained by Microtome and mounted on microscopic slides 213455555555555555555555

Radiographical Evaluation: Radiographical evaluation for osteogenesis (bone formation) and density of the head of embryos in both groups was done in digital radiograph in both lateral view and cephalic view with exposure values of: 68 KV, 5 mA, 13.000 MS, with a spot size of 0.25 mm2, and the target to sensor distance was 23cm. The x-ray machine used was Promax x-ray (Dimax 3, Planmeca).

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Biochemical Analysis: 2 ml of blood samples were taken through cardiac puncture, from all pregnant rats included in the present study, the blood samples were centrifuged in a universal 16 A centrifuge, and serum was obtained for ALP analysis.

Enzymes Analysis -Alkaline Phosphatase

Serums of studied groups (control and experimental) were analyzed by colorimetric method for ALPase activity according to the following reaction:

Phenyl phosphate → ALP/PH 10 → phenol + phosphate

The liberated phenol is measured in the presence of amin-4-antipyrine and potassium ferricyanide. The presence of sodium arsenate in the reagent stops the enzymatic reaction. The procedure was done according to the manufacturer's instructions (Biormeriex phosphate alkaline kit/ France)

Calculation:

(Reading of Sample - Blank)/ (Reading of Standard) ×Concentration of Standard (n)

The concentration of standard 20 KAV/10 ml.

Results

The results of histological features of tooth development are assessed in the experimental group including rats from treated mothers with 0.1 IU and with 0.5 IU of calcitonin) and in the control group coincidental with different periods of tooth development.

1- Prenatal life

a) At 16 days I.U.L.

Control group: shows tooth germ in the bud stage, enamel organ arises from dental lamina which extended from oral epithelium illustrates active basal cell proliferation with presence of basement membrane separates it from the dental papilla. Dental papilla shows proliferation and active mitotic division of ectomesenchymal cells. The dental sac shows active cell proliferation, condensation around bud germ, and active blood vessel formation as shown in Fig 1.

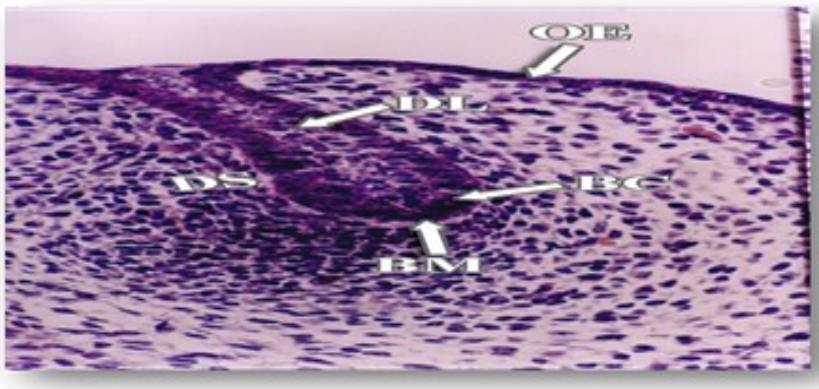

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Fig1. High magnification of the upper tooth germ of embryo rats (16 days I.U.L), control, shows Oral Ectoderm(0E), Dental Lamina (DL), Basal Cell (BC), Basement Membrane (BM) and Dental Sac(DS). H&E X 200.

Experimental group

(0.1 IU of Calcitonin): The histological findings of the coronal section include the upper and lower jaw of embryo rat at 16 days I.U.L. shows tooth germ in the cap stage. The Enamel organ differentiates into 3 layers include Inner enamel epithelium, Stellate reticulum, and Outer enamel epithelium.

The dental papilla shows active proliferation and condensation of ectomesenchymal cells beneath the inner enamel epithelium. The dental sac shows active cell proliferation, fibroblast cells can be detected. Active blood vessel formation can be noticed as displayed in Fig. 2.

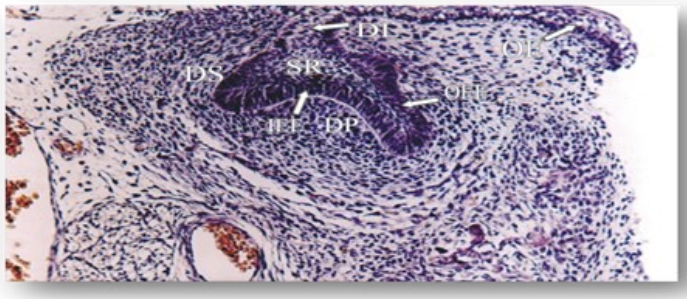

Fig.2: Coronal section in the upper and lower jaw of embryo rat (16 days I.U.L.), mother treated with 0.1 I.U of Calcitonin illustrates: A– Tooth germ of upper central in cap stage, Oral Ectoderm (OE), Dental Lamina (DL), Inner Enamel, Epithelium (IEE), Outer Enamel Epithelium (OEE), Stellate Reticulum (SR), Dental Papilla (DP), Dental Sac (DS). H&E X100

group (0.5 IU of Calcitonin): The microphotographic views of jaws for embryo rats at 16 days I.U.L. show an early stage of tooth germ development represented by the presence of primordium of thickening in certain areas of oral ectoderm. On high magnifying power the histological view illustrates active proliferative cells. Localized as a certain foci in oral ectoderm. The underneath tissue is the ectomesenchymal tissue as shown in bellow Fig. 3

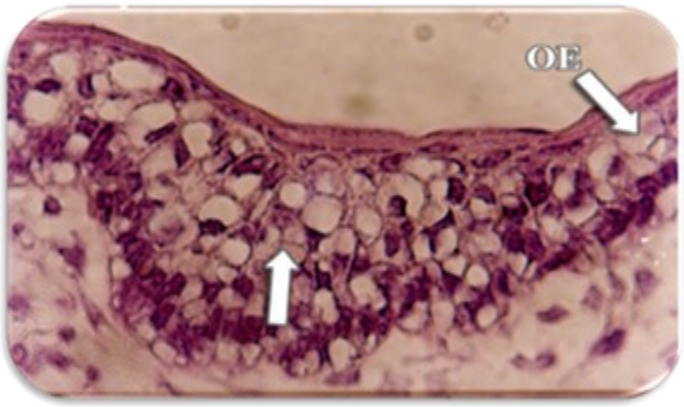

Fig. 3: High magnification shows: Active mitotic basal cells (arrow) representing early stage of tooth germ development, within the Oral Ectoderm (OE). Note theunderneath tissue is Ectomesenchymal Tissue (EMT). H&E X200.

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12b) At 18 days I.U.L.

Control group: histological findings of jaws of embryo rats 18 days I.U.L. shows tooth germ developed in the cap stage. The lower jaw illustrates the early cap stage. Tooth germ shows an enamel organ with 3 layers: Inner enamel epithelium as tall columnar cells in the concave area of the enamel organ. Outer enamel epithelium as cuboidal cells occupy the convex area of the enamel organ. The dental papilla shows active proliferative mesenchymal cells. The dental sac illustrates the condensation of the mesenchymal cell around the enamel organ as displayed in Fig. 4.

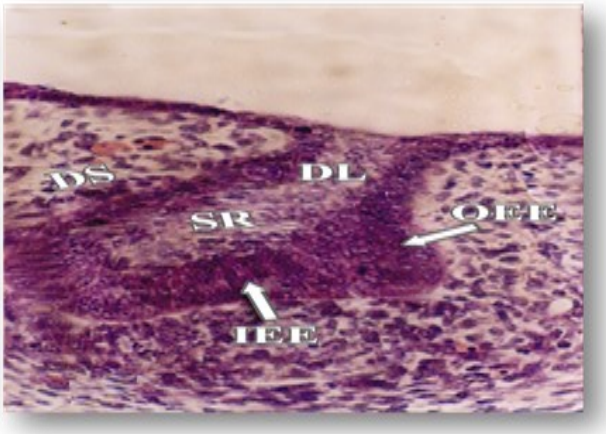

Fig.4: High magnification of tooth germ(control) of the embryo (18 days I.U.L) shows Inner Enamel Epithelium (IEE), Outer Enamel Epithelium (OEE), Stellate Reticulum (SR), Dental Lamina (DL), Dental Papilla (DP), Dental Sac (DS). H&E X200.

Experimental group (0.1 IU of calcitonin):

The microscopical findings of embryo jaws at 18 days I.U.L show tooth germ at the bell stage. The Enamel organ illustrates 4 layers including the inner enamel epithelium, the Stratum intermedium, represented by a few layers of the squamous cell lies over the inner enamel epithelium, the Stellate reticulum showed as stellate in shape and the Outer enamel epithelium. Fig.5 Cervical loop development can be detected, starting with root formation. Vestibule establishment can be also seen.

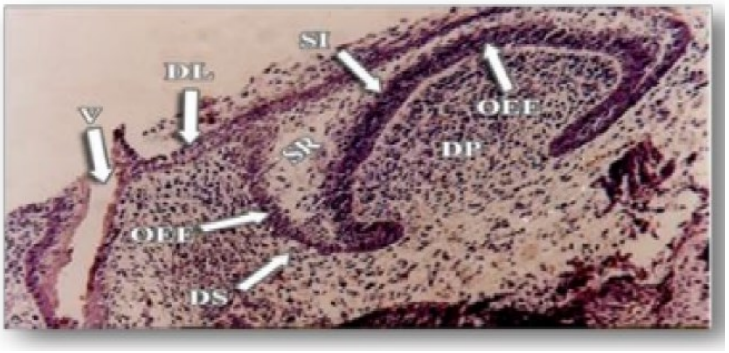

Fig.5: Microphotograph view of tooth germ for embryo rat (18- days I.U.L.), mother treated with 0.1 I.U of calcitonin. Illustrates tooth development at bell stage. Dental Lamina = DL, Inner Enamel Epithelium = IEE, Outer Enamel Epithelium = OEE, Stratum Intermedium = SI, Stellate Reticulum = SR, Dental Papilla = DP, Dental Sac = DS, Vestibule = V, H&E X100

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Experimental group (0.5 IU of calcitonin):

Histological findings of jaws of embryo rat (18 days I.U.L.) shows tooth development, suggested cap stage. The enamel organ shows inner enamel epithelium similar to outer enamel epithelium (tall columnar), stellate reticulum shows active proliferative cell, packed, condensed between inner and outer enamel epithelium. Dental papilla and dental sac show cells closed to inner enamel without separation, the cells also looked to show low proliferative activity. Fig.6.

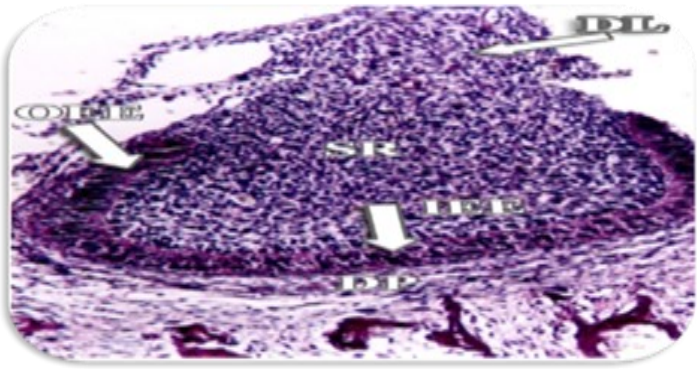

Fig.6: High magnification shows tooth germ layers, Inner Enamel Epithelium (IEE), Outer Enamel Epithelium (OEE), Stellate Reticulum (SR), Dental Lamina (DL), Dental Papilla (DP). H&E x 100

2- Postnatal life

At 1-day old rat.

Control group: Histological findings for tooth germ of one day old rat shows many events:

1. Histodifferentiation represented by odontoblast cell that deposits dentin and ameloblast cell that deposits enamel.
2. Morphodifferentiation represented by output morphology of tooth which shows to be incisors.
3. Fig.7 illustrates ameloblast cell tall columnar with Tom's process represented secretory phase.

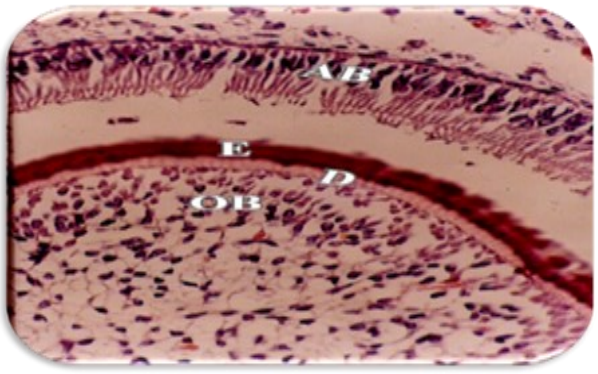

Fig.7: View for tooth germ of 1-day neonatal rat (control) shows Odontoblast (OB), Dentine (D), Enamel (E), Ameloblast (AB) with Tom's Process.

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Experimental group (0.1 IU of calcitonin):

Microphotograph view of tooth germ for embryo one day old shows hard tissue apposition (dentin and enamel). Fig.8 shows odontoblast cells occupy pulp surface, ameloblast cells occupy outer surface.

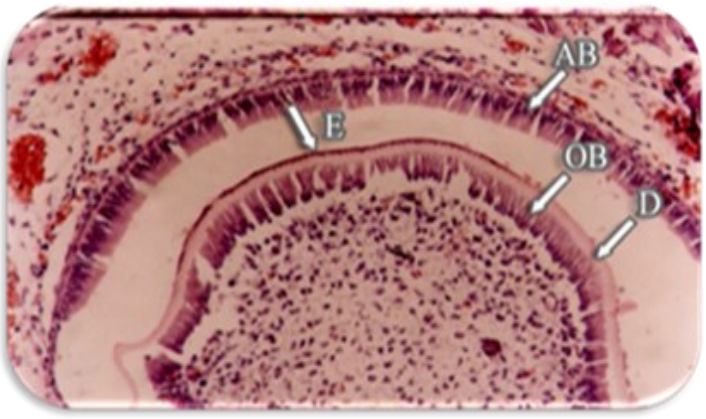

Fig.8: Microphotograph view of tooth germ for embryo rat 1-day old mother treated with 0.1 IU of Calcitonin illustrates hard dental tissue apposition (Dentine and Enamel) Pulp = P, Odontoblast = OB, Dentine = D, Enamel = E, Ameloblast = AB. (H& E X 100)

Experimental group (0.5 IU of calcitonin):

The histological findings of tooth germ of one day old rat shows, odontoblast cell differentiated from dental papilla, deposits of dentine (narrow zone). ameloblast cells show to be in their Presecretory stage. The pulp shows active mesenchymal cell, fibroblast cell, formation of new blood vessels. Fig. 9

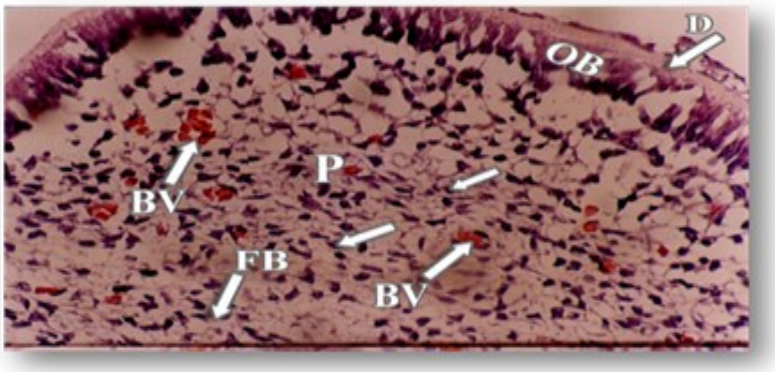

Fig.9: High power view for tooth germ related to embryo rat 1 day old treated with calcitonin (0.5 I.U) shows: Odontoblast (OB), Dentine (D), Pulp (P), active Mesenchymal Cell (arrow), Fibroblast Cell (FB), Blood Vessels (BV), H&E x 200.

b) At 10 days old rat:

Control group: the histological feature of tooth of rat (10 days old) shows complete deposition of hard tissue. The tooth surround by bony crypt, well developed bone formation which represented

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bone of the jaws. On high magnifying view, shows odontoblast, predentin, dentin, enamel, ameloblast in its Maturative stage as it represented microvilli in its distal end close to enamel. Fig.10.

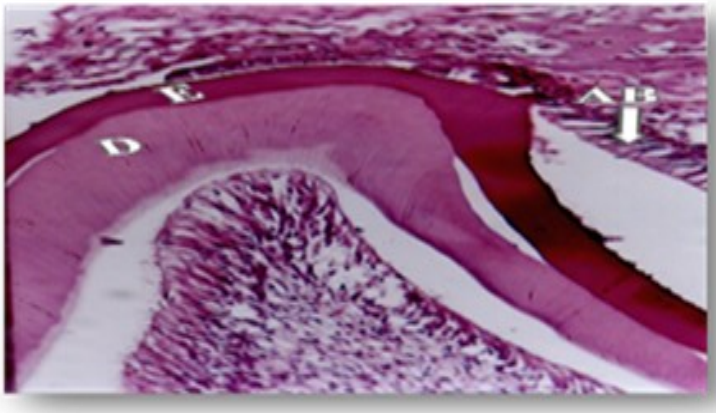

Fig.10: Microphotograph of the tooth germ of rat (10 days old) control, illustrated deposition of Dentin (D), Enamel (E), Ameloblast (AB) shows reduction in its size, H&E X 100.

Experimental group (0.1 IU of calcitonin):

Microscopical evaluation of tooth for rat (10 day old) shows apposition of hard tissue dentin and enamel. In Fig.11 High magnification shows Ameloblast still tall columnar in shape which still its secretory stage.

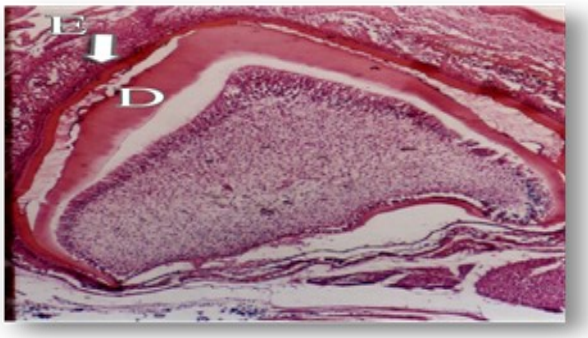

Fig.11: Microphotograph view for tooth germ of embryo rat 10 days old, mother treated with 0.1 calcitonin, illustrates apposition of Dentine (D), Enamel (E). H & E X 100

Experimental group (0.5 IU of calcitonin):

Histological findings of tooth related to rat (10 days old), illustrates deposition of hard tissue dentin and enamel, the tooth germ enclosed with hazy bone crypt represented by a thin trabecula.

High power magnification shows wide zone of predentin with irregular border line between predentin and dentine. Ameloblast secretes thin layer of enamel. Fig.12.

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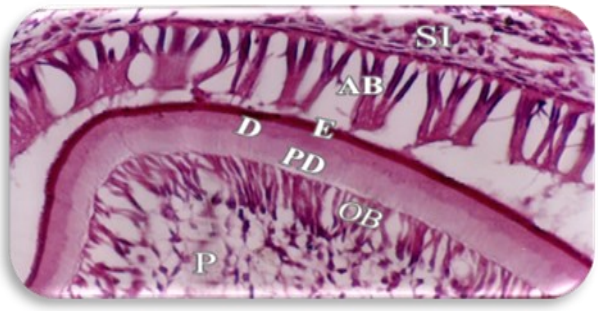

Fig.12: high power view shows Pulp (P), Odontoblast (OB), Wide layer of Predentin (PD), dentine (D), thin layer of Enamel (E) opposed by Ameloblast (AB). Note Stratum Intermedium (SI). H&E X 200.

Statistical analysis of hard structure width of central incisors in different group at 10 days old.

The statistical evaluation of the width of predentin, dentin and enamel were measured for studied groups (control and experimental) at time of calcification included (10 days old only). Statistical analysis shows significant value. No significant value was found in predentin thickness between control and experimental (0.1 IU) group. For dentin thickness, significant value was found in differences of the mean of width dentin between control and experimental (0.5 IU) groups while non significance difference was illustrated between control and experimental (0.1 IU) groups in dentin thickness.

Enamel thickness in experimental (0.5 IU) group shows thin layer deposit at 10 days old rat. statistical analysis for enamel width between control and experimental groups shows significant difference. Non-significant value in enamel thickness between control and experimental (0.1 IU) groups was recorded.

Radiographical Findings

Cephalic radiographic views and lateral radiographic figures are taken to embryos of treated mother with 0.1 IU and 0.5 IU of calcitonin. Age of embryo included 18 day I.U.L, 1-day old rat and 10 days old rat.

In comparison with control group matching same period of age, the results of radiographic film revealed low density of skeletal bone concerning to head region (especially maxilla and mandible, carrying the tooth germ), in the embryos treated (experimental groups). Differences radio opacity of bone illustrates easily between the study groups in different interval periods.

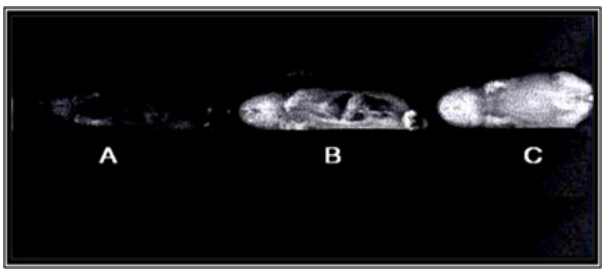

Fig.13: Lateral radiographic view of 1-day old rat represent:

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A- 1-day old rat from mother treated with 0.5 IU of calcitonin.
B- 1-day old rat from mother treated with 0.1 IU of calcitonin.
C- 1-day old rat control.

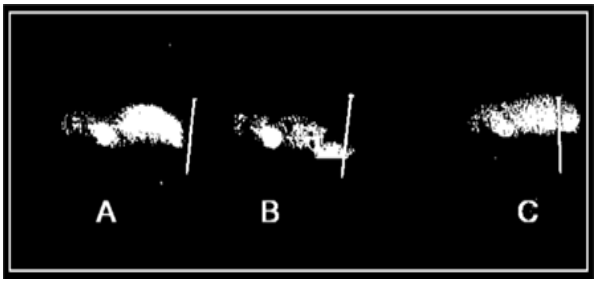

Fig.14: Cephalic radiographic view of 10-day old rat represent:

A- 10-day old rat from mother treated with 0.5 IU of calcitonin.
B- 10-day old rat from mother treated with 0.1 IU of calcitonin.
C- 10-day old rat control

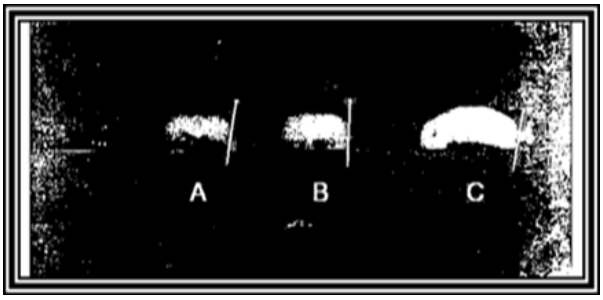

Fig.15 Lateral radiographic view of 18 days I.U.L embryos represent:

A- 18-day I.U.L. embryos from mother treated with 0.5 IU of calcitonin.
B- 18-day I.U.L. embryos from mother treated with 0.1 IU of calcitonin.
C- 18-day I.U.L. embryos control

Biochemical results:

Assessment of Alkaline Phosphatase enzyme (ALP) in serum of pregnant rat.

The mean concentration of ALP in serum of control group at different periods (16 day I.U.L, 18 day I.U.L and 1-day postnatal period) shows little variation in levels as (742.2+ 2.39, 744.8+- 2.3 and 742.8 +2.24) respectively.

In experimental group (0.1 IU) the level of ALP shows to be higher in 1 day period than in 16 day I.U.L and 18 day I.U.L (439.1+- 2.43, 207.9+- 4.06 and 218.8+- 2.19) respectively.

While in experimental (0.5 IU) group, ALP level shows to be higher in 16 day I.U.L than in 18 day I.U.L and 1 day postnatal (350.8+- 2.74, 289.1+-3.41 and 286.7+- 2.8) respectively, (Table 1).

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Table (1) Mean and Standard deviation of AIP. And ANOVA table

Study groups	16 day		18 day		1day		F-test	P-value	Sig
	Mean	SD	Mean	SD	Mean	SD			
Control	742.2	2.396	744.8	2.305	742.8	2.242	5.180	0.010	S
Exp.1(0.1)	207.9	4.061	218.8	2.199	439.1	2.433	280.4	0.000	HS
Exp.2(0.5)	350.8	2.748	289.1	3.411	286.7	2.840	218.4	0.000	HS

***P<0.05 Significant**

****P<0.0001 High significant**

Statistical analysis (ANOVA) of (ALP) mean concentration in serum among study groups of different interval periods

Statistical analysis t-test and p-value for each group between different periods (Table 2) records significant value in control group between 16 and 18 I.U.L periods and between 18 day and 1 day. While non-significant value shows between 16 I.U.L and 1 day in the levels of ALP.

For experimental (0.5 IU) group high significant values in differences of ALP concentration in comparison between 16 IU and 18 IU periods and 16 IU and 1-day periods. Non-significant value record between 18 I.U.L and 1-day periods.

Table (2) t-test between times of ALPase

	Control		Exp.1(0.1)		Exp.2(0.5)	
	t-test	P-value	t-test	P-value	t-test	P-value
16 &18	2.811	0.014 S*	8.055	0.000 HS	57.05	0.000 HS
16&1day	0.770	0.454 NS	182.7	0.000 HS	63.75	0.000 HS***
18&1day	2.523	0.024 S	236.2	0.000 HS	1.680	0.115 NS**

***P<0.05 Significant**

****P>0.05 Non significant**

*****P<0.0001 High significant**

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Statistical analysis (t-test) of serum (ALPase) level in study groups at different interval periods

Using ANOVA test (Table 3) revealed high significant variation among the study groups in serum ALPase level at different interval periods. And significant value in control group among different periods.

Table (3) Mean and Standard deviation of AIP. And ANOVA table

Study groups	16 days		18 days		1day		F-test	P-value	Sig
	Mean	SD	Mean	SD	Mean	SD			
Control	742.2	2.396	744.8	2.305	742.8	2.242	5.180	0.010	S
Exp.1(0.1)	207.9	4.061	218.8	2.199	439.1	2.433	280.4	0.000	HS
Exp.2(0.5)	350.8	2.748	289.1	3.411	286.7	2.840	218.4	0.000	HS

***P<0.05 Significant**

****P<0.0001 High significant**

(Table 4) illustrates t-test and p-value which shows high significant record in difference of concentration of ALPase between control and experimental (0.1 IU) group, control and experimental (0.5 IU) group and experimental (0.1 IU) and (0.5 IU) groups at different interval periods.

Table (4) t-test between times of ALPase

Study groups	16 days		18 days		1day	
	t-test	P-value	t-test	P-value	t-test	P-value
Control&exp.1(0.1)	424.3	0.000 **HS**	698.8	0.000 **HS**	320.2	0.000 **HS**
Control&exp.1(0.5)	386.4	0.000 **HS**	401.2	0.000 **HS**	446.6	0.000 **HS**
Exp.1(0.1)&exp.2(0.5)	114.9	0.000 **HS**	70.81	0.000 **HS**	145.1	0.000 **HS**

****P<0.0001 High significant**

Statistical analysis (t-test) of serum (ALPase) level in study groups at different interval periods

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Discussion

Prenatal Period

At 16 days I.U.L, embryos received 0.1 IU of calcitonin showed premature initiation of tooth germ, as the result illustrates tooth germ at cap stage incomparison to control which showed tooth germ at bud stage. While a deterioration in development of tooth germ was observed in experimental group that received 0.5 IU of calcitonin, represented as localized foci of epithelium thickening in oral ectoderm. This result could be explained by the effect of (0.1 IU calcitonin) as a chemical signal in initiating or participating in premature interaction between the epithelium of enamel organ (oral ectoderm) underneath mesenchyme of neural crest cell in origin, leading to the early development of tooth germ. Versus the action of 0.5 IU calcitonin which may act as an inhibitory factor for epithelial-mesenchymal interaction that deteriorates tooth development.

At 18 days I.U.L, the present findings showed the development of tooth germ in the cap stage in the control group while the experimental (0.1 IU of calcitonin) group developed in a bell stage. Two different stages of development morphogenesis and histogenesis, respectively.

The results may be attributed to the influence of 0.1 IU calcitonin dose on cell differentiation, illustrated by the formation of 4 distinct layers: inner enamel epithelium, stratum intermedium, stellate reticulum, and outer enamel epithelium. Also, the development of the cervical loop which initiates root formation and establishment of the vestibule, is indicated for early and faster evidence of development in comparison with control.

Postnatal period

The present study of embryonic incisor tooth germ of a one-day neonatal rat showed deposition of hard tissue, dentin, and enamel for both control and experimental (0.1 IU calcitonin) groups with histodifferentiation of both cell odontoblast and ameloblast cell, while in experimental (0.5 IU of calcitonin) group, only dentin deposition is illustrated, and the ameloblast seems to be in presecretory stage. Delay in histodifferentiation leads to delay in the deposition of specialized tissue, as a biological sequence due to the influence effect of that dose of calcitonin. [9]

At 10 days old rat, histological results for control showed complete deposition of hard tissue (enamel and dentin). The presence of microvilli in its distal end indicated of maturation stage of ameloblast in which typical morphology of absorptive cells was demonstrated in histological figures for transporting organic components as well as water from the matrix with the addition of minerals and growth of crystals [10].

For the experimental (0.1 IU calcitonin) group the histological examination revealed a complete deposition of hard tissue, enamel, and dentin, although the mean thickness of (predentin, dentin, and enamel) showed to be more than in control, but statistically with no significant value. The results may show that 0.1 IU dose, could not interfere with amelogenesis and dentinogenesis processes. [11].

While the experimental (0.5 IU calcitonin) group illustrated a wide zone of predentin with an irregular borderline, ameloblast secretes a thin layer of enamel as histological records revealed a

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significant difference in mean thickness of predentin, dentin, and enamel, in comparison to the control group. This result indicated impairment in the maturation process including the deposition of organic matrix represented by a thin layer of enamel formation and the mineralization process illustrated by decalcified dentin which is the predentin layer.

Radiographical Findings

Results of cephalic and lateral radiographic view showed low density of skeletal bone in treated embryos with calcitonin specially and severely with 0.5 IU, in comparison to control. These results supported the previous histological findings.

Biochemical Results

The present study provides data on levels of alkaline phosphatase enzyme: - serum of pregnant rat at 16 days I.U.L, 18 day I.U.L, and 1 day (equal to 21 day I.U.L). Unfortunately, we failed to get blood sample from rats of 10 days old because of their small size in a time concerning with mineralization process and the data above.

The present results showed that ALPase concentration in the pregnant rat of control illustrated a significant difference at interval periods 16 I.U.L, 18 I.U.L, and 1 day old while it showed a high significant value in differences of ALPase concentration between control and experimental group 0.1 IU and experimental group 0.5 IU.[12] reported that ATPase is essential for the deposition of minerals in the bone and teeth [13] revealed that developing teeth and bone showed a high enzyme activity, and noted differentiating odontoblasts, stratum intermedium, and in osteoblast cells.

This fundamental information explains the present result as the calcitonin dose (0.1 and 0.5 IU) used in this study showed a lower level of ALPase, therefore, it illustrated an impairment in bone formation as appeared histologically and radiographically.

Conclusion

1. Calcitonin hormone has an effect on both bone and teeth as the results showed histologically, radiographically, and biochemically.

2. Calcitonin of 0.1 IU dose showed an effect on developing bone more than teeth, concerning the impairment of the mineralization process.

3. Calcitonin of 0.1 IU dose was found to be an initiator for the tooth-developing germ as the results showed advanced stages of development in comparison to the control.

4. Calcitonin of 0.5 IU dose was found to be an inhibitor and showed deterioration effects to developing bone and tooth. As the results showed failure of complete maturation and calcification of tooth and bone in comparison to control and to Calcitonin of 0.1 IU dose.

5. Calcitonin showed to play role in alkaline phosphatase enzyme level, may affects its metabolism or/and its function and later on developing bone and teeth.

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Evaluation of Some Biochemical Parameters in Iraqi type 2 diabetes Patients

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Abstract

Diabetes mellitus is a class of metabolic problems where an individual has raised glucose, either because there is not sufficient insulin delivered by the pancreas, or because cells do not respond to the insulin generated. This study aims to evaluate some biochemical variables in humans with type 2 diabetes and their relationship to exacerbating the disease condition. Seventy patients suffering from diabetes mellitus and fifty healthy people were incorporated as should be expected controls for this review. Blood examination was done for every one of them which incorporate serum glucose, lipid profile, urea, creatinine and liver enzymes (ALT, AST, GGT) levels. This study included the verification of some biochemical variables by measuring their levels in diabetics and healthy people.

As the levels of all the variables under study increased in diabetics except for high-density lipoproteins, its level decreased compared to the results obtained for the same variables in healthy people.

Keywords: Diabetes mellitus, lipid profile, liver function, kidney function.

Introduction

Diabetes is a metabolic disease characterized by high blood sugar levels due to impaired insulin production or both. Chronic diabetic hyperglycemia is associated with relatively common long-term microvascular problems affecting the skin, kidneys, and nerves, as well as an increased risk of cardiovascular disease (CVD). The clinical criteria for diabetes are focused on glucose levels related to microvascular disease, in particular retinopathy [1]

The proportion of people with type 2 diabetes represents 90-95% of all diabetics, and it is the type that is not dependent on insulin. It usually affects people who have insulin resistance due to a defect in insulin receptors on cells or a lack of insulin secretion in proportions that do not make them need insulin therapy as cells Beta in the pancreas still secretes insulin [2]

Fat cells, liver cells, and muscles usually show insulin resistance compared to other body cells with type 2 diabetes patients.

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Most type 2 diabetes are obese with more than 20% of their ideal weight by calculating the Body Mass Index. People who are overweight have insulin resistance and therefore the pancreas must work hard to produce more insulin. However, the amount of insulin secreted will not be sufficient to maintain a normal level of blood sugar.

Type 2 diabetes can be controlled by controlling the type and amount of food and exercise and thus controlling weight. As the disease progresses, diabetes medications are needed.

To ensure control of the perfect diet and exercise, in addition to adhering to taking medications, it is advised to do the HbA1c test several times during the year that this test gives the average level of glucose during the life of red blood cells [3-5]

When the blood sugar level rises to the point where it appears in the urine, it will cause excessive urination, thirst, hunger, and disruption of protein and fat metabolism. [6]. Type 2 Diabetes is the major problem in developing and developed countries, It is considered one of the leading causes of mortality and ranks seventh among the other death-causing illnesses.

The diversity of diet systems and the lifestyles that differ in different countries and cultures have a great role in increasing the number of diabetics during the year and it is expected to reach about 300 million in the year of 2025 [7].

The complications caused by insulin deficiency are problems with metabolic disorders, which causes blood glucose to increase in addition to the high level of creatinine, cholesterol and transaminase enzymes accompanied by a decrease in the body proteins [8].

It was observed that secondary complications in diabetics are changes in the formation of the vascular basal membrane in addition to the accumulation of glucose and the products of the reactions that lead to an increase in the use of glucose in the insulin non-dependent tissues. [9]. Most studies confirmed that increasing blood sugar leads to an increase in serum glycated proteins [10-12] along with alterations in other atherogenic risk factors.

This study included an evaluation of some biochemical factors in type 2 diabetes patients and their comparison with the results obtained for healthy people.

Materials & Methods

Control Groups: The study included 50 healthy adults who did not suffer from any disease (females and males) as a control group.

Patients: The group of patients includes 70 patients with type 2 diabetes, their ages range from 20 to 70 years, and blood samples were taken from them after a 12-hour fasting period.

Full history and general physical examination were obtained from the patient's file.

Sample Collection: Venous blood samples were collected from the patient and placed in EDTA tubes, then separated using a centrifuge at 2000 rpm for 10 minutes. The samples were kept at -20 ° C until analyzed.

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The statistical study was performed on the data obtained and the outcome are expressed as mean standard deviation. To compare the outcome of the two groups under study, a T-test was used. If the value of P is equal to or less than 0.05, then these are significant differences.

The two group's distribution, depending on age and health status

Groups	No.	Age range (Years)
Normal	**50**	**22-60**
Type 2 DM Patients	**70**	**20-70**

Blood glucose measurement: The blood glucose concentration was measured after a fasting period (FBG) using the commercially available enzymatic chromatography method [13].

Determination of Serum Total Cholesterol and Serum Triacylglycerol by using an enzymatic method. [14].

Measurement of Serum High-Density Lipoprotein- Cholesterol (S.HDL-C)

Using the Burstein et al. process, 1980 [15] The serum HDL-C is determined by the HDL-C package.

Measurement of Low-Density Lipoprotein- Cholesterol (S.LDL-C) in serum

The LDL amount is most frequently extracted from the formula of friedwalds as mentioned [16].

LDL-cholesterol = Total cholesterol – [HDL- cholesterol + TG/5]

Measurement of Serum Urea

Urease enzyme hydrolysis urea by-product ammonium by (urease –modified Berthelot) reaction [17], by this method urea concentration, was measured.

Determination of Serum Creatinine

Creatinine was evaluated by the Jaffes reaction, in which creatinine was quantified with picric acid, which produces an orange color in alkaline medium; after a 15-min incubation at room temperature for color development, the color was measured at 520 nm.

Determination of Serum ALT, AST & GGT

The enzymes Alanine aminotransferase (ALT) and Aspartate aminotransferase (AST) were assayed by Reitman and Frankel method [18]. Gamma Glutamyl Transferase (GGT) was determined by SZASZ [19]

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Results and discussion

The study included seventy diabetics and fifty healthy people as a control group. The results obtained for diabetes patients were divided into two groups, females and males, due to the presence of some differences in biochemical parameters, and then compared with the control group.

Tables 1&2 show the levels of glucose of fasting control and diabetes patients. The results showed a high level of blood glucose in male fasting patients (175.4 ± 1.46) compared to the control group under the same conditions (88 ± 4.0) and this also applies to female results, where a high level of blood glucose was recorded (170.4 ± 1.65) compared to the control group of females who recorded (84 ± 4.2).

Table (1) Average fasting blood glucose level (FBG) (mg/dl) in the diabetic and control group.

Gender / FBG	Normal	Diabetics	p-value*
Mail	**88±4.0**	**175.4 ±1.46**	**<0.001**
Female	**84±4.2**	**170.4 ±1.65**	**<0.001**

* Significantly different at P<0.01 from the corresponding control value

The routine method for screening for diabetes is measuring blood glucose concentration; however, there are differences in blood glucose concentrations if measured randomly. [20], this is in addition to glucose intolerance by diabetics. This study showed an increase in the level of blood glucose in diabetics compared to the healthy group as agreed in all studies.

Tables 2 and 3 show the concentrations of lipid profile in diabetics and in healthy subjects, where total cholesterol showed an increase of 183.6 ± 35.9 mg/dl in addition to low-density lipoprotein LDL-C (155 ± 4.75 mg/dl) and triglycerides (39 ± 11.42 mg/dl) On the other hand, the results showed a decrease in the level of high-density lipoprotein HDL-C (21 ± 3.0 mg/dl). These results were compared with the results obtained for the same tests on the healthy group. Their levels were as follows cholesterol (**182.8 ± 34.1**), LDL-C (**155** ±4.75 mg/dl), triglycerides (**39** ±11.42 mg/dl) and HDL-C (24 ± 3.77).

Table (2) The mean of serum Total Cholesterol, HDL C, Triglyceride and LDL- Cholesterol levels (mg/dl) in diabetic and healthy groups (Males).

Biochemical Parameters(mg/dl)	Normal	Diabetics	p-value*
Total cholesterol	**182.8 ± 34.1**	**183.6 ± 35.9**	**0.658**
HDL cholesterol	**24 ±3.77**	**21 ±3.0**	**<0.001**

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Triglycerides	**30 ±13.42**	**39 ±11.42**	**0.006**
LDL cholesterol	**151 ±3.77**	**155 ±4.75**	**0.001**

Table (3) The mean of serum Total Cholesterol, HDL C, Triglyceride and LDL- Cholesterol levels (mg/dl) in diabetic and healthy groups (Females).

Biochemical Parameters(mg/dl)	Normal	Diabetics	p-value*
Total cholesterol	**192.9 ± 36.7**	**200.2 ± 36.2**	**0.001**
HDL cholesterol	**48.6 ± 11.7**	**45.8 ± 10.9**	**<0.001**
Triglycerides	**123 ± 86**	**161 ± (113–243.5)**	**<0.001**
LDL cholesterol	**119.7±3.27**	**122.2±4.65**	**0.001**

*Significantly different from corresponding control value at P<0.01

Metabolism pathways are generally controlled by many enzymes. In the case of diabetes, these pathways will be affected, including fat metabolism, through changes in the activity of these enzymes.

The increased incidence of death for patients with diabetes type 2 coincides with the myocardial infarction; the hyperlipidemia must be treated severely.

The most important signs of arteriosclerosis and coronary heart disease (CHD) are high levels of low-density lipoprotein cholesterol (LDL-C) lowering of its level decreases the worsening of the condition and death.

This study is consistent with the results of Sharma (1970) and Jain (1980) who demonstrated that high total cholesterol and triglyceride levels were increased with the reduction of LDL-C and HDL-C in the drug-treated group where the above substances were regulated and the lipid values were restored to normal levels [22,23].

The results in Table 4 showed urea and creatinine concentrations in normal and diabetic patients. In normal subjects, the concentration of urea (30.1±3.20) and creatinine (0.95±0.06) obviously, it is higher in diabetics (58.9±1.195), (1.96±0.109) than normal subjects.

Table (4) The level of Urea & Creatinine concentration (mg/dl) in DM patients and normal groups

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Biochemical Parameters(mg/dl)	Normal	Diabetics	p-value*
Urea	**30.1±3.200**	**58.9±1.195**	**0.001**
Creatinine	**0.96±0.067**	**1.96±0.109**	**<0.001**

Kidney function measured by measuring the levels of creatinine and urea in the blood, it is necessary to monitor their levels in diabetics because the kidneys can be exposed to failure due to diabetes and as shown, the level of creatinine and urea is higher in patients with diabetes compared to healthy people, so these results show the strong relationship between the blood sugar and urea levels.

High blood urea level is observed when the blood sugar level increases. High blood sugar level is the leading cause of kidney failure [24]. From these data, it is possible to confirm the relationship between high blood sugar level and high urea level, as shown in the results.

A study was conducted on diabetic mice by Anjaneyulu *et al.,* 2004 and it was found that the high level of urea and creatinine in mice serum caused kidney damage gradually [25]. Urea and creatinine levels decreased after treating diabetic patients.

Tables 5&6 show the concentration of ALT, AST, and GGT in normal groups and diabetic patients. In normal subjects the serum AST (**25 ±3.43**), ALT (**21 ±3.54**) and GGT (**30 ±4.02**) appeared to be higher in diabetic patients (**26 ±4.45**), (**24 ±4.43**) and (**39 ±4.50**) than normal subjects.

Table (5) The mean of serum ALT, AST & GGT levels (mg/dl) in Diabetes groups and normal groups (males)

Biochemical Parameters(units/l)	Normal	Diabetics	p-value*
AST	**25 ±3.43**	**26 ±4.45**	**0.089**
ALT	**21 ±3.54**	**24 ±4.43**	**<0.001**
GGT	**30 ±4.02**	**39 ±4.50**	**0.006**

***** It differs significantly from the corresponding control amount at P<0.01

Table (6) The mean of serum ALT, AST & GGT levels (mg/dl) in Diabetes groups and normal groups (females)

Biochemical Parameters(units/l)	Normal	Diabetics	p-value*

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AST	**22 ±3.46**	**23± 3.64**	**0.076**
ALT	**16 ±3.64**	**20 ± 3.34**	**0.001**
GGT	**15 ±4.32**	**20 ± 4.45**	**0.001**

*Significantly different from corresponding control value at P<0.01

This study showed the relationship between liver enzymes present in blood serum and type 2 diabetes. As the results showed that serum levels of ALT and GGT positive association with increased risk of type 2 diabetes and for both sexes in comparison to healthy subjects.

One of the major functions of the liver is to regulate metabolic processes and maintain glucose concentrations in all cases. When insulin is lost, its effect on the liver will lead to the activation of glycogenolysis to produce glucose from the liver and an increase in the process of lipolysis that leads to increased production of fatty acids.

The process of lipolysis and Abnormalities of triglyceride storage in tissues sensitive to insulin, such as the liver, is an early indication of cases that are described as insulin resistance and can be detected before fasting hyperglycemia.

The results regard to liver enzymes are agree with the results of previous studies [26,27], where they have proven high levels of alanine aminotransferase, aspartate transaminase, and GGT in diabetics in comparison to to healthy people. The reason is that the liver has been affected by an increase in fatty acid production that may lead to toxic effects on the liver.

Mechanisms may include disturbance of the cell membrane at high concentration, imbalance of mitochondria, the formation of toxins, Activating and inhibiting major metabolic processes. The oxidative stress of reactive lipid peroxide, peroxide beta-oxidation, and recombinant inflammatory cells are other potential reasons for the increase in transaminases in insulin resistance states.

Increased pro-inflammatory cytokines such as α-tumor necrosis factor (TNF-α) are associated with insulin resistance which may help to damage hepatocytes. We also assume that elevated ALT, a gluconeogenic enzyme whose gene transcription is suppressed by insulin, may indicate insulin signal impairment rather than injury to pure hepatic cells [28]. Another possibility for ALT elevation is due to weight gain [29].

Conclusion

The most common metabolic disease is diabetes mellitus and one of the main causes of death. It is known by a lack of insulin secretions in the pancreas from the beta cells, or insufficiency of insulin receptors on the cells, chronic hyperglycemia and metabolic disorders of carbohydrates, fats and proteins.

In our research, different biochemical parameters for normal and diabetic patients have been examined. In addition to T. cholesterol, TG, LDL, urea, creatinine, AST, ALT, and GGT, a high amount of fasting glucose was observed and the amount of high-density lipoprotein in diabetic patients decreased relative to the normal control group.

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Serum Level of IL-10 and IL-33 among Iraqi patients with sinusitis

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Abstract

Objective; objective of the present research is the evaluation of the roles of IL-10 and IL-33 indicators in pathophysiology of sinusitis patients

Methods; The conducted investigation occurred inside the capital Bagdad during time period from March to July 2022, thirty-six blood samples had from patients suffering from sinusitis that attending outpatients clinics after screening them by specialist physician. Additionally, thirty-two blood samples were collected from individuals without disease and considered them as control group. Study ages were ranged from 17 - 60 years All markers were quantified in all participants by utilizing enzyme linked immunosorbent assay (ELISA) with kits provided from Bio-Sources International (Camarillo,USA) Results of current investigation were calculated by SPSS v. 21.0 and Prism v.6 statistical software programs.

Results Findings of our investigation showed the age groups 30-50 years appeared highest percentages in patients (43.75%) and controls (50.00%). Our research showed the most patients were it found the most patients were females (62.5%) compared to males (37.50%)and controls (36.11% and 63.89%) Our results showed a highly significant increase ($P \leq 0.01$) in IL-10 level in patients compared to controls and a significant increase ($P \leq 0.05$) in IL-33 level was observed in patients compared to controls .It has been noted increased levels of IL-10 and IL-33 in patients ≤30 years and decrease levels in patients 30-50 and >50 years with significant differences ($p<0.05$).As for gender show increased levels of IL-10 and IL-33 in males higher than in females (127.61 ±4.01 , 16.22 ±1.68) and (124.29 ±1.56 , 15.97 ±2.08) respectively. don't showed significant differences ($p>0.05$) with gender patients.

Conclusion According to the study's findings, males had a higher incidence of sinusitis than females. Sinusitis patients had higher levels of IL-33 and IL-10 than controls, but as they grew older, their levels declined due to decreased protein synthesis, inflammation, organ dysfunction, and chronic illness. All of these traits play a part. IL-10 and IL-33 levels are decreasing with increasing age.

Keywords: sinusitis , IL-10, IL-33, , Iraqi

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Introduction

One of the most prevalent and significant serious issues is sinusitis, a condition that affects the mucous membrane in the sinuses and nasal cavity [1] Viruses, bacteria, and fungi are among the causes of sinusitis, and viruses with, as well as the presence of a number of bacteria that Parainfluenza virus, Rhino virus Importance and impact Staphylococcus aureus infects humans and causes inflammation, including Klebsiella pneumoniae and occurs in patients with a weak immune system [2], and among the types of fungi that cause sinusitis is Aspergillus Rhizopus [3]. It is divided into inflammation. Acute sinusitis causes inflammation of the respiratory system and includes a number of symptoms such as cough, nasal congestion, pressure and pain in the face, loss or difficulty of smell, and its duration is shorter from (12) weeks [4].

It i2s one of the common diseases in Iraq, according to global medical information, as it is the fifth disease among common diseases in Iraq, and studies have shown that the prevalence of sinusitis is 10.9% of the population of Europe [5], and in the United States it has shown that it is 11.9% of the population. The population has CRS with a peak prevalence (15.9%) in the 50-59 age group [6],

Chronic sinusitis is a recurrent infection that lasts for a period of time more than (12) weeks and is characterized by inflammation of the sinuses and nasal mucosa [7] The psychological condition of the patient is affected by chronic sinusitis, which is characterized by a set of symptoms and the presence or absence of nasal polyps (CRSwNP). These include headaches, ear pressure, olfactory impairment, and blockage of the nasal passages. The diagnosis is made by nasal endoscopy followed by a CT scan [8]. There are a group of factors that increase the chances of developing a sinus infection, such as smoking and some medical conditions, including the modern use of decongestant sprays. Long-term nasal blockage from polyps, a deviated nasal septum, asthma, some face-related disorders, allergies, and other conditions such lung cystic fibrosis, variations Anything that raises the danger of infection, such as flying, diving, or air pollution Sinusoids [9].

The immune system is a device specialized in defending the body against microorganisms such as bacteria, viruses, fungi, and parasites. Immunity includes the release of innate immunity (Complement Chemokines, Cytokines), which provides protection from infection with diseases or any foreign substance present in it. It produces antibodies as a response to infection [10]. Cytokines are proteins secreted by Immune cells These cells can perform multiple functions, such as transmitting intercellular signals through which the inflammatory response is regulated [11]. A member of the IL-1 cytokine family, IL-33 is a protein that triggers a Th2 inflammatory response [12]. IL-33 is crucial in controlling the immune system's reaction to inflammatory illnesses including asthma and rhinosinusitis [13]. IL-33 has been actively secreted in its entire length shape (amino acids, 1–27) through necrotic cell death, Cellular stimulation triggers ATP release or during tissue injury, it can act as an alarmin to warn the immune cells after damage to the endothelial and epithelial cells through infection, trauma or stress [14]. IL-33 releases happen mainly via the death of cells by contagious insults or response to allergens(alarmin) in many forms of the cells, such as epithelial or endothelial cells and macrophages [15]. The objective of current investigation is to know the roles of IL-10 and IL-33 in sinusitis patients.

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Materials and Techniques

Collected samples

The conducted investigation was occurred Baghdad during the period from March to July 2022, thirty-six blood samples had from patients suffering from sinusitis that attending outpatients clinics after screening them by specialist physician. Additionally, thirty-two blood samples were collected from individuals without disease and considered them as control group. Study ages were ranged from 17 - 60 years.

Techniques

The collected blood were separated using centrifuge (6000 rpm for five minutes) to get the serum. All markers were quantified in all participants by utilizeing enzyme linked immunosorbent assay (ELISA) with kits provided from Bio-Sources International (USA).

Statistical analysis

Statistical Analysis System –SAS (2018) software was used, the impact of the patient and control groups' differences in the research variables was determined. The t-test was employed to contrast means statistically. In the present investigation, the chi-square test was utilized to compare percentages (0.05 and 0.01 likelihood) statistically significant.

Results

1.Age and gender of study groups

Findings of our investigation showed the age groups 30-50 years appeared highest percentages in patients (43.75%) and controls (50.00%) with no significant variations ($p>0.05$) between study groups based on age groups.

According to gender, our research showed no significant variations ($p>0.05$) between gender and study groups. In contrast, the variations in percentages among patients and among controls, where it found the most patients were females (62.5%) compared to males (37.50%) and controls (36.11% and 63.89%) respectively (table 1)

Table 1: comparison between age and gender features with patients versus controls

			Groups			P value
			Control (n=36)	Patients (n=32)	Total	
Age groups	≤30	N	11	11	22	1.00 NS
		%	30.562	34.38	32.40%	
	30-50	N	18	14	32	0.502 NS
		%	50.00	43.75	47.10%	
	>50	N	7	7	14	1.00 NS
		%	19.44	21.85	20.59%	

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Gender	**Males**	**N**	23	20	43	0.502 NS
		%	63.89	37.50	63.24%	
	Females	**N**	13	12	25	0.869 NS
		%	36.11	62.50	36.77%	

NS: Non-Significant

2.Mean concentrations of cytokines within study groups

Our results showed a highly significant increase ($P \leq 0.01$) in IL-10 level in patients compared to controls (126.36 ±2.56 and 59.49 ±2.73) respectively, and a significant increase ($P \leq 0.05$) in IL-33 level was observed in patients compared to controls, (16.12 ±1.29 and 13.16 ±0.91) respectively (Table 2).

Table 2: comparative mean concentrations of IL-10 and IL-33 indicators between patients and controls

Group	Mean ± SE	
	IL-10 (pg/mL)	IL-33 (pg/mL)
Patients	126.36 ±2.56	16.12 ±1.29
Control	59.49 ±2.73	13.16 ±0.91
T-test	7.527 **	2.797 *
P-value	0.0001	0.0491

**** Highly Significant ($P \leq 0.01$)**

***** Significant ($P \leq 0.05$)**

3. Relation of immunological markers with age groups and gender of patients

Present outcomes mentioned increased levels of IL-10 and IL-33 in patients ≤30 years (131.92 2±6.74 a) and (18.01 ±2.40 a2) respectively , and decrease levels in patients 30-50 and >50 years (121.58 ±2.10 b , 16.44 ±2.05 ab) and (127.19 ±0.64 ab , 12.55 ±1.72 b) respectively with significant differences ($p<0.05$).As for gender show increased levels of IL-10 and IL-33 in males higher then in females (127.61 ±4.01 , 16.22 ±1.68) and (124.29 ±1.56 , 15.97 ±2.08) respectively. don't showed significant differences ($p>0.05$) with gender patients (Table 3).

Table 3: Relationship between Age groups and gender with the immunological parameters (IL-10 and IL-33) of patient's groups

Mean ± SE			
		IL-10 (pg/mL)	**IL-33 (pg/mL)**
Age groups	**≤30**	131.92 ±6.74 a	18.01 ±2.40 a
	30-50	121.58 ±2.10 b	16.44 ±2.05 ab
	>50	127.19 ±0.64 ab	12.55 ±1.72 b
	LSD	8.692 *	4.805 *
	P-value	20.0498	0.0351
($P \leq 0.05$)			

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Gender	**Males**	127.61 ±4.01	16.22 ±1.68
	Females	124.29 ±1.56	15.97 ±2.08
	T-test	7.116 NS	2.963 NS
	P-value	0.692	0.507
Non-Significant			

Discussion

A single the greatest frequent health issues that prompt medical attention worldwide is sinusitis, which also ranks among the main reasons for prescriptions for antibiotics. Individuals with sinusitis experienced up to 73 million days with minimal activity in a year, with a total of about $2.4 billion in immediate healthcare costs (not counting surgery or radiographic imaging). Furthermore, according to Shaikh, up to 14.7% of participants in a National Health Interview Survey reported having sinusitis in the twelve months prior [17]

According to the study's findings, sinusitis was more common in men than in women. These findings were consistent with those of Zielińska-Bliźniewska et al and Ravantara et al It has been hypothesized that variations in anatomic size, tobacco sensitivity, and hormonal variables raise a woman's overall risk of developing rhinosinusitis [18,19]. Because their sinus ostia are smaller, women may be more prone to blockage and consequent infection [20].

Similar findings were found in Zielińska-Bliźniewska et al study, which indicated a rise in sinusitis cases beyond the age of thirty [18]. Our findings were consistent with the high frequency of sinusitis reported by Alfallaj) in males aged 30 years and above [21]. Human bodies alter as we age. One such alteration is the nose, which becomes longer and starts to droop somewhat due to weakening surrounding cartilage. These modifications may result in a pathway that is smaller, which may lead to blockage and decreased airflow. According to earlier findings through the collected research, both the maxillary and ethmoidal sinus expand and develop between the ages of 0 and 20 years, when they reach their maximal developmental peak. There may be a noticeable drop in volume after 20 to 50 years. The volume decline is more noticeable between the ages of 50 and 65, and it accelerates even more after that [22]

The differences among studies based on age and gender are related to sample size (Table 1). Jiang et al showed increased levels of IL-33 and IL-10 in sinusitis patients than controls, [23] and these findings were compatible to results of present study.

Persons with chronic rhinosinusitis (CRS) often have persistent nasal mucosal inflammatory processes, with the potential development of nasal polyps (NP). Furthermore, inflammation caused by eosinophils is a characteristic shared by the majority of CRS with nasal polyps (CRSwNP) groups, and it is solely linked to the higher levels of IL-33 [23]. An IL-1 family cytokine is IL-33. It is a recently identified cytokine that is thought to be significant during tissue destruction linked to necrosis as well as when inflammatory is activated. Tissue-derived nuclear cytokines IL-33 is frequently produced in the epithelial cells throughout inflammatory processes and homeostasis. It is increasingly thought to be important for the etiology of CRSwNP as well as the progression of fibrosis

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or ailments, inflammatory conditions, and allergic conditions in generalLike the airways epithelium's initial line of defence towards pathogens and stimulants, IL-33 is generated. This can cause strong allergic inflammatory conditions and act as "bridges" between both adaptive and innate airways mucosa immunity. By applying these inflammatory mediator regulators to the medical management of allergic rhinitis (AR), chronic rhinosinusitis (CRS), asthma, and allergies, a thorough examination of these epithelium-derived triple inflammatory mediators will reveal a deeper comprehension of the principles fundamental type 2 respiratory inflammatory conditions [24]. According to recent research, sufferers had greater levels of IL-33 than controls, but there were no distinctions in tissues types taken from CRSsNP and CRSwNP sufferers [18]. Likewise, Song et al. reported no variation in IL-33 levels between individuals with non-eosinophilic CRSwNP and those with eosinophilic CRSwNP [25]. According to Imoto et al., IL-33 is thought to raise 15-lipoxygenase 1 levels in acute myeloid (eosinophilic) leukemia cells, a substance that is known to promote inflammatory processes in eosinophilic CRSwNP patients [25] . On the other hand, it was discovered that blocking IL-33 in a mouse model decreased the overall thickness of the oedematous mucosa, the number of Th2 cells, and the amount of subepithelial collagen. Asthma individuals' higher blood levels of IL-33 have also been validated by other investigations [26].

Additionally, it was recently shown that anti-IL-33 antibodies have therapeutic promise against allergic rhinitis [27]. In addition to dramatically reducing symptoms, these antibodies may also lower Th2-type mediators and eosinophil counts in bronchoalveolar lavage (BAL), which in turn lowers nasal discharges. This clinical observation can also be applied to IL-33's potential as a treatment for human allergies. Overall, the results of this research support earlier studies in the same area, suggesting that Th2-dependent illnesses that include allergic rhinitis are influenced by IL-33 [28].

According to Oka et al., IL-10 is a cytokine with anti-inflammatory properties that plays a crucial role in immunoregulatory processes and is implicated in inflammation and allergy disorders [29]. According to Kang et al., prior research has shown that irregular levels of IL10 are present in nose discharge fluid, the nasal2 mucosa, and peripheral blood of the two types of animals and humans with allergic rhinitis (AR) and are linked to the onset and progression of AR [30]. The frequency of innate IL10+ lymphoid cells and their activation by IL10 were shown to be correlated with the effectiveness of allergen-specific immunotherapy (AIT) in individuals with residential dust mite allergy disease [31].

Over time, the pathophysiology theories about the role of cytokines that are inflammatory in CRSwNP have changed. While eosinophilic infiltration and a Th2 cytokine milieu continue to play a major role in the formation of polyps, current research has brought attention to the involvement of additional cytokine subpopulations of IL-10 aids in preserving the state of inflammation by preventing the synthesis of inflammatory substances linked to pathogens. In contrast, TGF-β is a key factor in CRSwNP's pro-fibrotic activities.2 When together, these inflammatory cytokines strengthen the Th2 a microenvironment, which causes CRSwNP to have a distinct and intricate profile [32].

The investigators propose that IL-10 inhibits the generation of reactive oxygen species (ROS), inflammatory processes, and fibrosis. Additionally, by suppressing the downregulation of hyperpolarization-activated cyclic nucleotide-gated potassium channel 4 (HCN4), IL-10 may be a significant factor in preventing hyperglycemia-induced sinus node dysfunction (SND). Furthermore,

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STAT3 phosphorylation is necessary for IL-10-mediated suppression of p38 [33]. Prior findings suggest that increased IL-10 might be crucial in mitigating the effects of underpinning inflammation caused by allergies in allergic respiratory disorders; however, there was no discernible variation in the total amount of the mediators among the various kinds of patients. Thus, it is possible for authors to hypothesize that IL-10, an inhibitory cytokine, had a role in preserving an instance of health in wh8ich there is no inflammatory [34].

The pathogenesis of eosinophilic chronic rhinosinusitis (ECRS), which includes eosinophilia and deeper airway drainage, may be made worse by the results reported by the authors that nasal polyp (NP) reduced IL-10 generation in reaction to Staphylococcus aureus enterotoxin B (SEB) [35].

The cytokines of the IL-10 family have a variety of roles in CRSwNP, including responses to GCs, effects of allergens, and the epithelium. They may also be infected by viruses or bacteria. There haven't been many clinical trials using cytokines from the IL-10 family to treat airway inflammation. Consequently, [36] suggest that IL-10 family cytokines may be beneficial therapeutically in CRSwNP.

Finally, IL-10 and IL-33 were working in opposite, IL-33 is pro-inflammatory cytokine which lead to increase inflammation (activate immunological mediators and immune cells), while IL-10 is anti- inflammatory cytokine that lead to reduce inflammation and decrease secretions of respiratory tract (table 2).

According to effect of gender of sinusitis patients on levels of IL-10 and IL-33, present findings not reveals significant effect of males and females on levels of these cytokines , Finally, we found decrease levels of IL-10 and IL-33 in sinusitis patients with age progression due to reduce protein synthesis, inflammation, organ dysfunction, and chronic diseases [37] All of these features play role in reduce levels of IL-10 and IL-33 with age increasing (table 3).

Conclusion

According to the study's findings, males had a higher incidence of sinusitis than females. Sinusitis patients had higher levels of IL-33 and IL-10 than controls, but as they grew older, their levels declined due to decreased protein synthesis, inflammation, organ dysfunction, and chronic illness. All of these traits play a part. IL-10 and IL-33 levels are decreasing with increasing age.

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Determination of levels of Transferase enzymes, Alkaline phosphatase, Cholesterol and Bilirubin, associated with hepatic disturbances in patients presented to laboratories in Baquba-City

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Abstract

This cross–sectional study included 200 individuals, 15 males of one year, 25 females of one to 5 years old, 100 males of 10-73 years, and 60 females of 15-73 years, presented to official and private laboratories in Baqubah - City, during the 2023 year. Blood samples were collected upon which some biochemical constituents related to hepatic disturbances were determined, including transferase enzymes, serum bilirubin, serum alkaline phosphatase, cholesterol, serum total protein, albumin, urea nitrogen, and creatinine. The results showed that mean values of alanine aminotransferase were high in young males, and adult males, and females, the highest was in adult males. There is significant variance between young and adults and between males and females. The mean of aspartate aminotransferase was high in young females, and adult males and females. Means of alkaline phosphatase was high in the adult males and females. The mean of total bilirubin was high in all groups, direct bilirubin was higher than normal in adult males and females. Means of indirect bilirubin were within normal, cholesterol values were within normal. total protein low in young females, globin level high in adult males albumin level was high in young males. In conclusion, ALT was high in young males, while AST was high in young females. ALT, AST ALP, and direct bilirubin were high in adult males, and females. Total bilirubin levels were high in all groups. indirect bilirubin, cholesterol was within normal. total protein low in young females, globin level high in adult males albumin level was high in young males.

1. INTRODUCTION

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The liver is a large complex organ, that has a role in many functions, some of these are of metabolic, digestion, and get rid of the body from harmful elements [1,2]. Liver frequently suffering from a huge number of diseases which are often be difficult to confirm, as the symptoms easily confused with others health problems [3]. In facts many enzymes and the end products of the metabolic pathway occurring in the liver and very sensitive for these abnormalities which occurred, so may be regarded as biochemical markers of liver dysfunction. A series of special tests carried out on blood can frequently determine whether the liver functions normally or not. These tests can also differentiate the acute or chronic liver disturbances and between hepatitis and cholestasis [3]. Through such tests we can evaluate, the liver function (LFTs), from which, Transferase enzymes both Alanine and Aspartate (AST, ALT), Alkaline phosphatase (ALP), serum total bilirubin (TB), direct bilirubin, indirect bilirubin, lactate dehydrogenase, total protein, globulin, and albumin [1, 4].

These constituents are aminotransferase (ALT, AST), Alkaline phosphatase (ALP), and prothrombin. Alteration in the levels of these enzymes may be a signal to hepatic injury or interference with bile flow [5]. Changes in these elements, either accompanied with symptoms appeared in hepatic disease, or a local, non-expected finding in a patient suffering from a non-hepatic disease or for minor, vague complaints [5].

The excretion of anions was represented by the level of bilirubin, while transaminases reflected the degree of hepatocellular integrity, meanwhile, formation, and the flowing of bile measured by levels of bilirubin and ALP, and protein synthesis was indicated by the level of albumin [6]. Means and median values of ALP were higher in adult female and male groups, and within normal in young males and females. ALP is elevated with cholestasis [7].

In healthy individuals, biochemical signals pointed to hepatic injury often one of challenging faced even for experienced physicians, that lead to set off a battery of further, costly tests [8]. The aim of this study was estimation of elements and enzymes that reflect the hepatic state in patients suffering from one or more of hepatic disturbances.

2. MATERIALS AND METHODS

The study is cross-sectional and includes 200 patients, 15 males of one year (Group I); 25 females of one to 5 years (Group II); 100 males of 10- to 73 years (Group III); and 60 females of 15 to 73 years old (Group IV); presented to private and official laboratories in Baquba City, Diyala province, during 2023 year. They were either apparently normal or suffered from one or more of diseases related to hepatic disturbances. Blood was drawn to estimate some of the enzymes and elements related to liver disturbances, including alanine, and aspartate aminotransferase; bilirubin; alkaline phosphatase; cholesterol; protein; albumin; blood Urea nitrogen; creatinine, these were evaluated by colorimetric assay using automated analyzer (Bioreux, London) apparatus [9].

2.1 Statistical Analysis

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Descriptive statistics for continuous variables were presented as Mean ± Standard error, as frequency and proportions (Percentage) for categories. T-test was used to compare the resultant between groups. < 0.05 was considered a significant level [10].

3. Results

Means of ALT values in groups I, III, and IV, were higher than normal (40.30 ± 5.43; 224.79 ± 31.97; and 189.98± 34.84) respectively. The highest was in G III, followed by G. IV. While in G II was within normal (33.03± 3.66). There were significant variations between young (G.I and II, P<0.05) and adult (G.III and IV, P<0.05), and between male and female groups. The percent was higher in male groups (G.I and III) In G.I; 7 /10 (70%) and G.III 55/66 (83.3%) cases showed higher, than in female G. IV 29/50 (58%) higher, 1/50 (2%) lower. and in G.II 1/13 (7.7%) lower and 5/13 (38.5%) higher than the normal limit. Median values were higher than normal in G. I, III, and IV (37.2; 146 and 87) respectively and were within normal in G.II (33.35) as shown in Table 1.

Means of AST in G. I was within normal (24.29 ±2.77); while in G. II, III, and IV were higher than normal (179.87±139.26; 214.96 ±27.76 and 198.90 ± 6.89) respectively there were significance differences in Gr. III and IV P<0.05) in comparison with other groups. The ranges in G. I only 1/10 (10%), G. II 4/23 (21.74%), G.III 28/47 (59.6%) and G.IV 19/38 (50%). The median in G.I, II, and IV were within normal (24.8; 29.55, and 35.5), but in G.III was higher (79) as shown in Table 1.

Means of ALP were within normal in groups I, and II (68.06 ± 11.11; and 99.43± 23.20). Those from groups III, and IV were higher, the highest was in G.III (406.15 ± 53.31 and 262.03± 28.12, P<0.05). The ranges in G.I. were lower in one case (11.11%), and higher in one case (11.11%); while in G.II two cases were lower (11.76%) and 4 cases (23.53%). In G. III one case lower (2.44%) and 29 (70.73%) higher, G.IV showed 27 higher (71.05%). The median values were within in G.I, II and higher in G.III and IV (62.72; 60.08; 256 and 156) as shown in Table 1.

Table 1 Levels of aminotransferase and alkaline phosphatase

Param.	Gr	M± SE	Range	Low.	High	Med.	Refer.
ALT u/l	I	40.30 ± 5.43 a	10.5-71.1	-	7/10 (70%)	37.2	10-35
	II	33.03 ± 3.66 a	7.67-52.76	1/13 (86.92%)	5/13 (38.46%)	33.35	

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	III	224.89± 31.97 bc	10.0-1750	-	55/66 (83.33%)	146	
	IV	189.98 ± 34.84 b	9.1-987	1/50 (2.0%)	29/50 (58.0%)	87.0	
AST u/l	I	24.29 ± 2.77 a	15.28-40.58	-	1/10 (10%)	24.8	0-40
	II	28.10± 3.66 a	6.11-94	-	4/23 (17.39%)	24.8	
	III	214.96± 27.76 bc	13-965	-	28/47 (59.57%)	79	
	IV	198.90 ±6.89 b	14-921	-	19/38 (50%)	36.5	
ALP u/l	I	68.06 ±11.11 a	33.74-139.47	1/9 (11.11%	1/9 (11.11%)	62.72	35-129
	II	66.02 ± 10.01 a	20.2-152.48	1/13 (7.69%)	1/13 (7.69%)	60.08	
	III	406.15 ± 53.31 bc	14-1900	1/41 (2.44%)	29/41 (70.73%)	235	
	IV	262.03 ±28.12 b	55-1350	-	27/38 (71.05%)	156	

M± SE; a, b, c, significance, between groups

Mean of total bilirubin were higher than normal in all groups (1.72± 0.46; 3.98 ± 2.01; 5.73 ±0.45 and 3.47± 0.233, P<0.05) respectively. Range in G. I, 2/10 (20%) high, in G. II, 6/15 (40%) high, and 5/15 (33.23%) low, G.III 47/61 (77.05%) high, and in G.IV 39/61 (63.93%) higher than normal. The medians were within normal in G.I and higher in those from other groups (0.9; 1.07; 6.7 and 2.0). Table-2-

The means of direct bilirubin were higher than normal in G.III and IV (5.49± 0.81; and 5.27± 0.55). The ranges in G.III 3/323 (0.38%), low and 16/32 (50%) high, In G.IV 3/31 (9.68%) low and 18/31 (58.06%) high. Median high in G.III (4.2) and within in G.IV (0.39) table-2-

Means of indirect bilirubin were within normal in G.III and IV (0.82 ± 0.20 and 0.59 ± 0.04). The range is 2/13 (15.38%) in G.III and one /19 (5.26%) high. The medians were within normal (0.58 and 0.58) Table-2-

Table 2 levels of Bilirubin (Total, Conjugated, Unconjugated)

Param.	Gr	M± SE	Range	Low.	High	Med.	Refer.
T.B. mg / dl	I	1.75 ± 0.46 a	0.5-12.0		2/10 (20%)	0.9	0.3-1.0
	II	3.98 ± 2.01 b	0.13-18.0	5/15 (33.33%)	6/15 (40%)	1.07	

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	III	5.73± 0.45 b	0.5-45		47/61 (77.05%)	6.0	
	IV	3.47 ± 0.33 b	0.4-73		39/50 (78%)	2.0	
D.B. mg/dl	III	5.49 ± 0.81 a	0.02-16.8	3/32 (9.38%)	16/32 (50%)	3.9	0.1-0.4
	IV	5.27 ±0.55 a	0.02-16.79	3/31 (9.68%)	18/31 (58.06%)	0.39	
I. B. mg / dl	III	0.82 ± 0.20 a	0.33-3.13		2/13 (15.38%)	0.58	0.1-1.0
	IV	0.59± 0.04 a	0.29-1.03		1/19 (5.26)	0.58	

M± SE; a, b, significance, between groups

Ranges, Median of cholesterol, were within a normal; total cholesterol (1.36 ±0.13; 1.45 ± 0.21; 2.06 ± 0.08 and 1.30± 0.12). Median (1.17; 1.29; 1.98 and 1.27) as shown in Table 3. HDL cholesterol, was within normal, in those from G.III and IV (55.26 ± 1.38; 49.0 ±3.51). The ranges of 3 cases in G.III and 4 cases in G.IV were higher. The medians were lower than normal (55; and 49) as presented in Table 3. VLDL – cholesterol was higher in G.III (42.25± 6.52), and within (26.25± 4.31) in G.IV; 2 cases in G.III high. Medians were higher in G.III and within G.IV (51 and 33) as shown in bellow Table 3. Levels of LDL were between (133.73±8.46; and 73.4±15.23). Range one case in G.III high; 3 in G.IV low. Median were within in G.III and low in G.IV (138.9; 68.2) as shown in bellow table.

Table 3 Levels of different types of cholesterol

Param.	Gr	M± SE	Range	Low.	High	Med.	Refer.
T. chol. mg/dl	I	136± 13	85-187			117	<=190mg/dl
	II	145 ± 21	22-281		1/6	129	
	III	206± 8.26	191- 229	-	4/4	189	
	IV	130±11.82	107- 163	4/4		127	
HDL	III	55.26 ± 1.38	43-66		3/19	55	35-55mg/dl
	IV	49.0± 3.51	40-59		4/12	49	
LDL	III	133.73± 8.46	117.2-2145.1		1/3	138.9	70-140 mg/dl
	IV	73.4 ± 15.23	52.5-117.9	¾		68.2	
VLDL	III	42.25 ±6.52	27-55		2/4	51	<=40mg/dl
	IV	26.25± 4.31	15-33			33	

M± SE; a, b, c, significance, between groups

Serum protein was within normal, G. I, low in G.II (66.70± 0.30; 59.22± 0.67). Rangers 3 cases (421.86%) in G.I. low and 8 (61.54%) in G.II low; one case (7.69%) high. The median was within normal in G. I, and low in G.II (6.845; 5.734) as shown in Table 4. Globin levels were higher in G.III, than G. IV (163.63 ± 51.126; 141.08± 11.82). 4/19 (21.05%), in G.III, high; 2/12 in G. IV. Median were higher in G. III (130; 140) as shown in Table 4. Albumin levels were higher in G. I, and within in G. II (5.81± 0.10;

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5.11± 0.53); G.III (5.04± 0.24; G.IV 4.66 ±0.29). Ranges 8 cases higher, and one case lower in G. I and 8 in G.II, higher. Median was higher in both groups (> 60; 5.31; 4.9; 4.3) as shown in Table 5.

Table- 4 - Levels of Total protein, albumin and globulin

Param.	Gr	M± SE	Range	Low.	High	Med.	Refer.
T.P. g/dl	I	6.67 ±0.30	5.67-7.95	3/7 (42.86%) B		6.85	6-8
	II	5.92 0.67	3.07- 8.78	8/13 (61.54%) bc	1/13 (76.92%) A	5.73	
	III	6.04± 0.21	4.5 – 8.2	8/19 (42.11%) A	1/19 (5.26%) A	6.3	
	IV	5.06 ±0.05	3.5 -6.8	9/12 (75%) A		4.6	
Albumin g/dl	I	5.81± 0.10	5.31->6.0		8/8 (100%) Bc	>6.0	3.5-5.0
	II	5.11± 0.53	2.97 - >6.0	1/13 (7.69%)	9/13 (69.23%) B	5.31	
	III	5.04± 0.24	3.6- 7.9		8/19 (42.11%)	4.9	
	IV	4.66± 0.29	3.5-6.9		5/12 (41.67%)	4.3	
Globin mg/dl	III	163.63 ±51.16	71-414		4/19 (21.05%)	130	<=200
	IV	141.08 ±11.82	89-210		2/12 (16.67%)	140	

Table 5 Levels of Creatinine and BUN

Param.	Gr	M± SE	Range	Low.	High	Med.	Refer.
Creatinine mg/dl	I	0.85± 0.06	0.57-1.05		4/9 (44.44%)	0.99	0.5-0.90
	II	0.71 ±0.06	0.38-1.11	1/13 (7.69%)	4/13 (30.77%)	0.63	
	III	0.73± 0.02	0.6-0.9	6/28		0.7	

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				(21.43%)			
	IV	0.73± 0.05	0.6-0.9			0.7	
BUN mg/dl	I	9.63± 0.59	8.35-12.85			9.07	7-22
	II	7.08± 0.60	3.37-10.11	7/13 (53.85%)		6.84	
	III	29.21± 1.33	19-39		16/19 (84.21%)	29	
	IV	25.25 ± 1.79	16-32		9/12 (75%)	26	

M± SE; a, b, c, significance, between groups

4. Discussion

Approximately 8% of the general population, are suffering from abnormal LFTs. Which is transient in apparently healthy, not showing symptoms patients, about 30% of these elevations, resolving after three weeks [11, 12].

In this study, means and median, values of ALT, were higher than normal in most groups, the highest levels were in the adult male group. In females was within normal. Means of AST, were higher in most groups, particularly in adult males. Generally, ALT is the parameter that changes in acute and obstructive hepatic injury. While AST changed in chronic and infiltrative lesions of the liver [13]. ALT is found in high concentrations as it is specific and a cytosolic enzyme in the liver [14]. Individuals with liver dysfunction and reduced aminotransferase show insignificant fibrosis histologically [15].

The results revealed that there were significant variations in values of aminotransferase and ALP, in young and adults, as the result of the study, showed the highest level in adult males, followed by adult females, then young males, and lastly young females. There were variations in the percentage of highest or lowest, as it was higher in adult and young males in comparison with those of adult female. This indicated a variation according to age, six. Levels of aminotransferase differ according to sex and age, and their levels may increase with strenuous exercise [16]. Aminotransferase ALT and AST are good indications for liver damage. Values of each aminotransferase are high in normal males in comparison with females [17]. Also associated with obesity with a natural range for comparison higher in those of high body mass index [18].

The result of acute or chronic hepatic injury is elevation of serum aminotransferase concentration. AST is present in isoenzymes of cytosolic and mitochondrial; liver, myocardium, skeletal muscles, brain, pancreas, lungs, kidneys, Erythrocytes and Leukocytes [14]. In this study means and median values of ALP were higher in adult female and male groups, and within normal in young males and females. ALP is elevated with cholestasis [7]. Principally the main two sites of ALP in the body, liver and bones. The diseases which are the common causes for its rise. Other sites from which ATP may originate include the placenta, kidneys, intestines, and leucocytes. Elevation may be physiological or pathological [14].

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The late stage of pregnancy, and adolescent have a correlation with the elevation of ALP in serum, as they are main sources of it [16]. ALP elevated with cholestasis. If bilirubin and ALP elevated in disproportion to ALT and AST this is characterize a cholestatic state. Transferases are elevated with hepatocytic injury, as their elevation in out of proportion to ALP, and bilirubin denotes a hepatocellular disease [19]. Abnormal levels of ALP indicator of malignant liver tumor, lymphoma, or infiltration disease as sarcoidosis [14, 20]. In present study mean of total bilirubin were higher in all groups, while median was within only in young male and higher in other groups. Conjugated bilirubin was higher in adult male and females; while unconjugated bilirubin were within normal in adult females and males.

The less frequent cause for unconjugated hyperbilirubinemia included resorption of large size hematoma, or inactive erythropoiesis [14]. In healthy peoples, direct bilirubin in serum is not of importance as a result of rapid bile secretion [19]. It rises, in case of loss of half of the liver ability of excretion, so its increases are signs of liver disease. Hyperbilirubinemia in conjugation with significant rises in transferase, may indicate acute viral hepatitis or hepatic damage, due to toxic agents, or in ischemia, in addition to autoimmune hepatitis [20]. Cholestasis accompanied by hyperbilirubinemia rises in ALP, simple rises in transferase may occur in cholestasis as a result of drug reaction [21].

Serum bilirubin is normally in an indirect form, reflecting a balance between production and hepatobiliary excretion. Production of indirect bilirubin increases in hemolysis, ineffective erythropoiesis, resorption of a hematoma, and rarely in muscle damage. If conjugated with hyperbilirubinemia, this indicated hepatocellular injury and biliary obstruction [6].

The results of study, showed that means of total protein, were within normal in all groups. While means of albumin values were higher in groups I and II, and within normal in groups III and IV. The actual function of the liver can be graded based on its ability to produce albumin as well as vitamin K dependent clotting factors [3, 19, 22].

Decreased serum albumin signifies decreased hepatic synthetic ability. However, albumin does not decrease with advanced liver fibrosis. So, albumin do not appear to be, a good measure, of hepatic fibrosis [12]. Cirrhosis due to many diseases is associated with diminished numbers of hepatocytes and thus decreased hepatic capacity to synthesize albumin. albumin is produced by liver cells, but it is not one of the specific liver tests, as albumin; levels in serum may lowered in patients with urination syndrome, malabsorption, loss of protein through intestines, or MA nutrient. Decreased serum albumin is induced by many diseases [9].

The results showed that mean values of globulin were the highest in G.II, and within normal in other groups. The mean and median values of total cholesterol, HDL, and LDL; were within normal in all groups. While values of VLDL were higher in adult males, and within normal in adult females. LDH is commonly included in biochemical liver panels but has poor diagnostic specificity for liver disease. Markedly increased LDH levels are observed in hepatocellular necrosis, shock liver, lymphoma, or hemolysis associated with liver disease [23].

5. Conclusions

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There were individuals suffering from hepatic injury, on the dependence of elevation of values of constituents, mainly ALT, ALP, and bilirubin. ALT was high in young males, while AST was high in young females. ALT, AST ALP, and direct bilirubin were high in adult males, and females. Total bilirubin levels were high in all groups. indirect bilirubin, cholesterol was within normal. total protein low in young females, globin level high in adult males albumin levels were high in young males. It is necessary to carry out a general screening study to estimate the normal levels of blood constituents to be used as references in local Iraqi studiers, and by clinicians in hospitals.

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Clinical assessment of glycated hemoglobin in diabetic hypothyroid patients: A comparison with Euthyroid non diabetic subjects

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Abstract

Background: Thyroid disease and diabetes mellitus (DM) are the two most common heterogeneous endocrine disorders in the general population. Both hypothyroidism and type 2 DM are closely involved in cellular metabolism and affect the malfunction of various organ systems. HbA1c was studied for its correlation with thyroid hormones and used for screening, diagnosis, and control of glycemic status.

Objective: To evaluate the validity of HbA1c as a screening and useful test to diagnose hypothyroid patients with pre-diabetes and diabetes.

Methods: The current study was conducted in the Specialized Center for Endocrinology and Diabetes/Baghdad, Iraq from October 2021 to May 2022. The present study was carried out on 115 hypothyroidism patients (92 females and 23 males), and one hundred individuals with normal thyroid function were chosen as a control group. Each patient and individual was investigated for thyroid profile using Vitek immunodiagnostic assay system (VIDAS), while HbA1c was assessed on whole blood by automated chemistry analysis (Analyticom).

Results: The results showed that most hypothyroid patients were within the age group (24-70) years, which represented 20% ≤(30), 32.2% ≤(40), and 28.7% ≤(50) years. Most hypothyroidism patients were females constituting 80% compared with 20% for males. Most hypothyroidism patients were obese BMI≥30Kg/m² represented 42.7% and overweight ≥ 25Kg/m² represented 40% compared with 15.7 who were normal weight. The prevalence of diabetes mellitus represented more than two times among the hypothyroidism individuals compared with the control sample, which indicated a highly significant relationship at Pvalue<0.01. The results also showed that meaningful significant differences were revealed between the two independent groups with highly significant differences at Pvalue<0.01 within the following parameters (HbA1c, Glucose, Thyroid stimulating hormones (TSH), Thyroxine (TT4), Triiodothyronine (TT3).

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Conclusion: The present study conclude that the frequency of diabetic patients was significantly increased in hypothyroid population when compared with general population. The use of HbA1c for screening and supported diagnosis assay is necessary to detect and control diabetic patients.

Keywords: Hypothyroidism, Thyroid hormones glycemic status, HbA1c.

Introduction

The two endocrinopathies thyroid disorder (TD) and type 2 Diabetes mellitus (DM) are significantly coexisting and excess and defect of any one result in systemic derangements in metabolic processes [1]. Thyroid hormones are correlated with insulin action, both insulin and thyroid hormones play crucial roles in the regulation of cellular metabolism [2]. In an underactive thyroid (hypothyroidism), there is reduced in the degree of glucose homeostasis, compared with euthyroid subjects. Liver gluconeogenesis, liver glucose output, glycogen synthesis, and deterioration lead to increased glycogen levels. Besides that, Beta cells produce the biological hormone insulin in the blood the half-life will be prolonged with an elevated level and decrease in insulin synthesis. Type 2 DM is a heterogeneous multifactorial disease caused by relative insulin inadequacy, condition of insulin resistance, and insulin receptor irregularities. In type 2 diabetes mellitus death of beta cell apoptosis is blocked caused by infections or chemicals induced [3,4]. The diagnosis of diabetes mellitus is classically based on blood glucose levels either fasting or 2-h plasma glucose (2hpG) after an oral glucose tolerance test (OGTT) using 75g anhydrous glucose [5]. The investigative standards of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) have released new guidelines on the management of hyperglycemia in patients with type 2 diabetes mellitus (T2DM). The criteria consist of either fasting plasma glucose (FPG) 126 mg/dl (7mmol/L) or more or 2hpG 200 mg/dl (11.1mmol/L) or greater [6, 7]. Using HbAc1 as a diagnostic test with a threshold of ≥6.5% because the HbA1c has several advantages to the FPG and OGTT including glycemic status over the past 2-3 months and it is not affected by the biological variability, lifestyle measures, and pre-analytical variability like FPG or OGTT [8]. The main disadvantages are affected by hemoglobinopathies and recent hemolysis. Testing to detect type2 diabetes and pre diabetes in asymptomatic people should be considered in adults of any age who are overweight or obese (BMI ≥25 kg/m²) and who have one or more additional risk factors for diabetes [9,10]. Therefore, diabetic patients need to be screened for thyroid dysfunction and assess the hyperglycemic effect by correlating fasting serum glucose and thyroid profile parameters [11-12]. The present study aims to examine the frequency of diabetes mellitus in patients with hypothyroidism and to assess the effect of diabetes on thyroid hormone levels and other biochemical variables in some Iraqi populations. In addition, a thyroid function test was studied for correlation with HbA1c.

Subjects and Methods

This comparison study was conducted on a group of 115 hypothyroid patients (92 females and 23 males), whose ages ranged between (24-70) years in Baghdad city. Patient samples and control subjects were collected at the Department of Specialized Center for Endocrinology and Diabetes, for the duration period from October 2021 to May 2022. All participants in this study were recruited and went through an examination for thyroid function; [total thyroxin (TT4), total triiodothyronine (TT3), and thyroid-stimulating hormone (TSH)].

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One hundred euthyroid individuals with no history of thyroid dysfunction detected or any other disease were observed and selected as a control group. Age and gender were statistically matched for patient group control. Personal biodata collection, record clinical history, and medical examination were collected and designed on pro-forma assessment for this study.

Fasting venous blood glucose (FBG) samples were aspirated with period a of 12-hour fasting for analysis of glucose level and lipid profile. Estimation of glucose levels was carried out by enzymatic colorimetric assay (GOD-PAP) test kit supplied by Biomaghreb [13]. About 5 ml of venous blood was drowned by a vacuum disposable syringe, (2 ml) of this blood was mixed with an anticoagulant EDTA vial tube, then mixed gently using a blood shaker to avoid clotting of the blood. Whole venous blood was obtained for estimation of HbA1c using an automated clinical chemistry analyzer [14]. Blood serum was isolated by centrifuging at 3000 R.P.M, for 10 minutes and transferred into a clean tube, and frozen at(-20c˚) For analysis of thyroid profile, serum thyroxine (TT4), triiodothyronine (TT3) and thyroid stimulating hormone (TSH) was measured by using VIDAS analyzer, which depends on enzyme-linked fluorescent assay (ELFA) [15,16].

Results and Discussion

Table (1): Statically distribution of the studied samples according to Gender and Age variables with Comparison of Significance

Variable	Groups	Samples		C.S. (*) P-value
		Study	Control	
Age (years)	20 -	10.4%	18%	Chi-Sq. test P=0.092 NS
	30 -	20%	13%	
	40 -	32.2%	31%	
	50 -	28.7%	21%	
	60 -70	8.7%	17%	
44.01 ∓ 10.7	44.7 ∓ 13.0	t = 0.412 P=0.680 NS		
Gender	Male	20%	25%	F.E.P. test P=0.237 NS
	Female	80%	75%	
Female / Male (1 : 1.33)				

(*) **Non significant at P>0.05**

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Table (1) displayed the relationship between the two groups according to age, the result indicated that there were non-significant differences at P>0.05 for the distribution of age groups between the two samples. In this study, 115 patients were diagnosed with hypothyroidism, their ages ranged between (24 and 70) years, as well a control group was obtained, whose ages ranged between (24–and 70) years. These results were in agreement with other studies [17,18,19]. The two most clinically significant changes in endocrine activity during the elderly comprised the pancreas and thyroid gland. Approximately 40% of individuals aged 65 to 74 years and 50% of those older than 80 years have impaired glucose tolerance or diabetes mellitus [20]. Age-related thyroid dysfunction is also common, lowered T4 and increased thyrotropin concentration occurs in 5% to 10% of elderly women [21]. These abnormalities are mainly caused by Autoimmune disease [22].

Relation between gender & hypothyroidism

Table (1) shows the association between the two groups according to gender, the outcome presented that there was a non-significant difference at P>0.05 for the distribution of gender between the two samples rather than (Female / Male) reported (1: 1.33) times at the (study/control) samples respectively. In the study group, males were (n=23) 20%, and female were (n=92) 80%, while in the control group, males were (n=25) 25% and female were (n=75) 75%. These results were extremely reliable for the studied groups since gender variable had corresponding similar distributions at each group. These results agreed with other studies [23,24]. Hypothyroidism is more common among women due to disturbance in reproductive hormones, mainly estrogen and progesterone [25].

Table (2): Statically distribution of the studied samples according to BMI and with Comparison of Significance

Variable	Groups	Samples		C.S. (*) P-value
		Study	Control	
BMI	Underweight < 18.5	0.90%	1.00%	Chi-Sq. test P=0.143 NS
	Normal weight 18.5 - 24	15.70%	27.00%	
	Overweight 25 - 29	40.9%	26%	
	Obese-1 30 - 34	27.0%	34%	
	Obese-2 35 - 39	7%	6%	
	Obese-3 ≥ 40	8.7%	6%	
29.5∓6.8	28.8∓6.04		t = 0.404 P=0.880 NS	

(*) **Non significant at P>0.05**

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Table (2) shows the association between the different groups according to BMI, the result revealed that there was a non-significant difference at P>0.05 for the distribution of BMI groups between the two samples. In the study group, BMI ranged between (17.0 and 57.0), whereas the control BMI ranged between (18.0 and 46.0).

The current study confirmed previous findings by different studies [26, 27]. Body mass index depends on the stability between food intake and total energy consumption. Energy consumption is processed mainly by physical activity and (REE) represents resting energy expenditure. The life span depends on the equilibrium of these factors [28,29].

Table (3): Descriptive statistics of the studied parameters for the two independent groups (Study and Control)

Parameters	Samples	No.	Mean	Std. Dev.	Std. Error	95% C.I. for Mean		Min.	Max.
						L. B.	U. B.		
HbA1c	Study	115	7.37	1.80	0.17	7.04	7.71	4.6	12.7
	Control	100	5.87	0.71	0.07	5.73	6.01	4.3	7.5
Glucose	Study	115	6.61	2.92	0.27	6.07	7.15	3.7	21
	Control	100	5.79	0.92	0.09	5.60	5.97	4	10
TSH	Study	115	22.34	19.35	1.80	18.77	25.92	5.4	60
	Control	100	2.24	1.23	0.12	2.00	2.49	0.3	4.9
T4	Study	115	71.31	24.18	2.25	66.85	75.78	61	115
	Control	100	84.10	12.10	1.21	81.70	86.50	56	108
T3	Study	115	1.36	0.49	0.05	1.27	1.45	0.3	2.3
	Control	100	1.56	0.38	0.04	1.48	1.63	0.9	2.3

Table (3) shows the descriptive statistics of the studied parameters for the two independent groups (study and control) as follows:

1- HbA1c parameter showed that with the study group, the mean value and 95% C.I. of the population mean value falls outside the normal range (4.5 – 7.0) % at the upstairs bound, and however that some of the original readings were normal. With respect of the control group, the mean value and 95% C.I. of the population mean value fall inside the normal range.

2- The glucose parameter showed that with the study group, the mean value and 95% C.I. of the population mean value falls outside the normal range (3.6 – 6.3) mmol/L at the upstairs bound, however, some of the original readings were normal. With respect to the control group, the mean value and 95% CI of the population mean value are fully inside the normal range.

3- TSH parameter showed that with the study group, the mean value and 95% C.I. of the population mean value falls outside the normal range (0.25 – 5.0) µIU/ml at the upstairs bound, however, some of the original readings were normal. With respect to the control group, the mean value and 95% CI of the population mean value are fully inside the normal range.

4- The T4 parameter showed that with the study group, the mean value and 95% C.I. of the population mean value fall inside the normal range (60 – 120) nmol/ml at the upstairs bound. With respect of the control group, the same results were reported as in the study group.

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5- T3 parameter showed that with the study group, the mean value and 95% C.I. of the population mean value falls inside the normal range (0.92 – 2.33) nmol/ml at the upstairs bound. With respect of the control group, the same results were reported as in the study group.

Table (4): Outcomes of testing differences between the two independent groups (study and control) at the studied parameters

Parameters	Levene's Test for Equality of Variances		t-test for Equality of Means			C.S. P-value
	F	Sig.	t	d.f.	Sig. (2-tailed)	
HbA1c	59.4	0.000	8.2	153.8	0.000	HS
Glucose	28.9	0.000	2.9	139.3	0.005	HS
TSH	238.3	0.000	11.1	115.1	0.000	HS
T4	28.6	0.000	-5.0	172.6	0.000	HS
T3	8.10	0.005	-3.4	210.1	0.001	HS

HS: Highly Significant at P<0.01; NS: Non Significant at P>0.05

Table (4) shows the results of testing hypotheses according to equality of variances and equality of mean values. The results of testing indicated that there was a highly significant difference at P<0.01 within the following parameters: (HbA1c, Glucose, TSH, T4, T3).

The correlation between the two samples

Table (5): Statically distribution of the studied samples according to the Diabetics variables with Comparison of Significance

Variable	Groups	Freq. & Percents%	Samples		C.S. P-value
			Study	Control	
HbA1c	Normal	Freq.	17	30	F.E.P. test P=0.006 HS C.C.=0.181 P=0.007
		HbA1c	36.2%	63.8%	
		Samples	14.8	30.0%	
	Abnormal	Freq.	98	70	
		HbA1c	58.3%	41.7%	

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		Samples	85.2%	70.0%	HS
Odds Ratio			Control/Study (1: 0.405)		
Glucose	Normal	Freq.	75	81	F.E.P. test P=0.007 HS C.C.=0.174 P=0.010 HS
		Glucose	48.1%	51.9%	
		Samples	65.2%	81.0%	
	Abnormal L. b.	Freq.	40	19	
		Glucose	67.8%	32.2%	
		Samples	34.8%	19.0%	
Odds Ratio			Control/Study (1: 0.440)		

HS: Highly Significant at P<0.01

Table (5) shows the distribution of the two samples according to different diagnoses (normal and abnormal) towards Hypothyroidism disease and Diabetics Mellitus (HbA1c and Glucose) parameters. The results were corresponding non-proportionally distributed and indicated a highly significant relationship at P<0.01, which indicated that patients with Hypothyroidism disease have more chance of being diabetic. In addition to that, an odd ratio was reported, which indicates that the prevalence of Diabetes mellitus represented more than two times the Hypothyroidism individuals compared with the control sample.

The current work showed the prevalence of diagnostic diabetic patients among some Iraqi hypothyroid patients and that diabetic women were more frequently affected than men. These results were in agreement with a number of reports on hypothyroidism and type 2DM [30,31,32]. While other study by Swamy et al (2012) there was significant percentage emphasize that the diabetic patients to be followed up with thyroid profile. The presence of chronic diabetic directed to drift towards hypothyroidism [33]. The reason for this outcome is that the thyroid gland which produces thyroxine (T4) and triiodothyronine (T3) are insulin antagonists that also encourage the action of insulin indirectly [34].

Table (6): Statically distribution of the studied samples according to Hypothyroidism Functions and with Comparison of Significance

Variable	Groups	Samples		C.S.
		Study	**Control**	P-value
TSH	**Normal**	**0.0%**	**100%**	**F.E.P. test P=0.000 HS**
	Abnormal	**100%**	**0.0%**	
T4	**Normal**	**73%**	**98%**	**F.E.P. test**

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	Abnormal L. b.	**27%**	**2%**	**P=0.000 HS**
Control/Study (1: 18.2)				
T3	**Normal**	**74.8%**	**95%**	**F.E.P. test P=0.000 HS**
	Abnormal L. b.	**25.2%**	**5%**	
Control/Study (1: 6.5)				

Table (6) displays the study samples to elucidate the hypothyroidism functions (normal & abnormal). The results reported that TSH parameters revealed a high significant difference at P>0.01 compared with the control group, and high significant differences were reported at P<0.01 with T4 & T3 parameters. These results were in agreement with a number of recent studies [35,36,37]. Research by Singh et al (2011) found the serum levels of TT3 and TT4 were significantly lower in diabetic subjects, while level of serum TSH was significantly higher in diabetic subjects [38,39]. The present study reported various levels of abnormal thyroid hormones in study groups of some Iraqi populations. This alteration may be an outcome of the various medications received**,** by patients for example Levo-Thyroxine and Insulin [40, 41].

The HbA1c or glycosylated hemoglobin test provides a good picture of the average blood sugar levels over a few months, giving access to diagnosis and monitoring of type 2 diabetes. However, certain biological factors and analytical factors could prevent this test from giving accurate results. These several risk factors or conditions affect the result of the HbA1c being falsely lowered or falsely elevated [42].

Limitations

The main limitation of this current study are the need to increase of the sample sizes. Another limitation of the current study there are conditions in which the HbA1c test is not a dependable origin for diagnosing diabetes, including, anemia, Iron deficiency, kidney disease, HIV, thalassemia, sickle cell disease, hemolysis, pregnancy, and blood transfusion.

Conclusion

1- Patients with age range between (30-50) years showed a high prevalence of hypothyroidism when compared with other age group.

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2- Primary hypothyroidism was more common in females than males.

3- The frequency of diabetic patients was significantly increased in the hypothyroid population when compared with the general population.

4- We conclude from this study that the use of HbA1c for screening and supported diagnosis assay is necessary to detect and control diabetic patients.

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