

Interferon-Gamma: Has Acromegaly and Diabetes an Impact on Such Marker?

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Abstract

Background: Acromegaly is a rare endocrine disease, its incidence is 4-6 per million per years while its prevalence is 40-60 per million. The distinctive facial characteristics are prognathism prominent forehead, and large hands and feet. This happens after the fusion of growth plates; separating acromegaly from gigantism that occurs before growth plates are closed. Interferon-gamma was checked in (80) acromegalic patients (50% are diabetics and 50% are non-diabetics) while (40) persons were regarded as healthy control group being non-diabetic, non-acromegalic. **Aim of the Study:** To find out impact Interferon-gamma in diabetic acromegalic *versus* non-diabetic acromegalic patients. **Methods:** Eighty acromegalic subjects were enrolled in across sectional study by measuring the level of Interferon-gamma in the sera of diabetics and non-diabetics as 39 are diabetics while the remaining 41 patients are non-diabetic. **Result:** Interferon-gamma is high among diabetic acromegalic patients when compared with non-diabetic acromegalic subjects. **Conclusion:** Interferon gamma is high in acromegalic diabetic patients, nondiabetic acromegalic patients, and controls (100%, 97.6%, and 97.5%, respectively). Interferon gamma is elevated in patients with acromegaly only in the age group of 30–39 years, but in those with diabetes, the elevation is noticed later within the age group of 40–49 years as if concomitant diabetes delays its elevation.

Keywords: Acromegaly, diabetic mellitus, interferon-gamma

INTRODUCTION

Acromegaly is a hormonal disorder that develops when your pituitary gland produces too much growth hormone during adulthood. When you have too much growth hormone, your bones increase in size. In childhood, this leads to increased height and is called gigantism. However, in adulthood, a change in height does not occur. Instead, the increase in bone size is limited to the bones of your hands, feet, and face, and is called acromegaly.^[1] Growth hormones are involved in inhibiting the function of insulin, like inhibiting the phosphorylation of insulin receptors, among the most significant aspects of insulin production. As a result, the insulin sensitivity of the cells will decrease, encouraging peripheral glucose absorption in the periphery, and increasing resistance to the gluconeogenesis suppression ability of insulin. Hence, the increase in growth hormone production leads to the mobilization of free fatty acids and avoids insulin-induced glucose oxidation, resulting in further deterioration of insulin resistance,

contributing to diabetes mellitus (DM).^[2] Oral glucose tolerance test-glucose has a suppressive neuroendocrine signal which reduces GH.^[3] In this test, 75 g of glucose is given at various points over a period of 120 min with GH measurements.^[4] Interferon-gamma (INF- γ) reported to play a vital role in innate and adaptive immune responses. Mainly, it was found to be a vital orchestrator of immune responses to viral infections, but it was soon realized that its immune-modulating activities achieved much greater and broader levels.^[5,6] A broad range of biological functions are performed by the downstream INF- γ signaling pathway target genes, which are mainly associated with modulation of innate and adaptive immune responses in host defense

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against viral and bacterial infections, but are also linked to cell cycle regulation, apoptosis, and inflammation.^[6] INF- γ directly controls the differentiation, activation, and homeostasis of T-helper-1 (Th1) cells in adaptive immunity; inhibits the production of Th2 cells; enhances the ability of regulatory T-cells (Treg); promotes the activity of natural killer cells; and activates inflammatory macrophages of the classic M1 subtype.^[7,8] INF- γ also plays an essential role in attracting particular effector cells to various inflammatory microenvironments by inducing various chemokines.^[9]

MATERIALS AND METHODS

Through the period from October 2020 to March 2021, 120 patients registered in the National Diabetes Center (NDC)/Mustansiriyah University were enrolled in the study, 80 acromegalic patients (40 – diabetic and 40 – nondiabetic) and 40 healthy controls; their control was defined by achieving the goals (pituitary adenoma, size regression, IGF-1, and GH decrement down to the recommended and predefined targets). They were subdivided into subgroups according to their age, disease duration, the use of Gamma-Knife radiosurgery, concomitant diabetes, and glycemic control in diabetic patients.

Interferon-gamma was studied by the use of enzyme-linked immunosorbent assay (ELISA), and the utilized ELISA was sandwich methodology. The Micro Elisa strip plate provided in this kit has been precoated with an antibody specific to INF- γ and study the correlation between INF- γ and other biochemical and clinical variables was studied using the suitable statistical methods.

The SPSS Statistics for Windows, version 27. 0 (SPSS Inc., Chicago, Ill., USA) was utilized to analyze the data.

RESULTS

Eighty acromegalic patients were recruited, of which 40 are diabetics and the other 40 are nondiabetics, while the control group includes 40 nondiabetic, nonacromegalic healthy persons.

All the recruited patients are registered in the NDC/Mustansiriyah University.

Table 1 and Figure 1 show that INF- γ is high in all acromegalic patients but only 97.6% and 97.5% of nondiabetic acromegalic patients and healthy controls, respectively.

Table 2 shows that interferon-gamma is high among diabetic acromegalic patients followed by nondiabetic acromegalic patients and finally the control group.

Interferon-gamma is the highest in the age group of 40–49 years among the diabetic acromegalic group and 30–39 years among the nondiabetic acromegalic group and the control group.

Interferon-gamma is found to be higher in males in diabetic acromegalic, nondiabetic acromegalic patients, while in the control group, there is no gender difference.

Interferon-gamma is found to be higher in diabetic acromegalic patients in those with disease duration <10 years, but in nondiabetic acromegalic patients, it was found to be higher in those with acromegaly duration >10 years.

In diabetic acromegalic patients, INF- γ is higher in Gamma-Knife-treated diabetic acromegalic patients versus those who were not treated by Gamma-Knife. However, in nondiabetic acromegalic patients, the use of Gamma-Knife has no impact on INF- γ , as shown in Table 3.

INF- γ in statin users and nonusers shows nonsignificant difference in the diabetic acromegalic, nondiabetic acromegalic, and control groups, however, it was found to be the highest in diabetic acromegalic, nonstatin users.

The level of high-density lipoprotein (HDL) has no impact on the level of INF- γ among the three groups.

High cholesterol is associated with marginal nonsignificant elevation of INF- γ in diabetic acromegalic patients only.

Something that attracts attention is the significant reduction of INF- γ in diabetic acromegalic patients when their triglyceride is high, thus increasing triglyceride is associated with reduction of INF- γ ($P = 0.017$), as shown in Table 4.

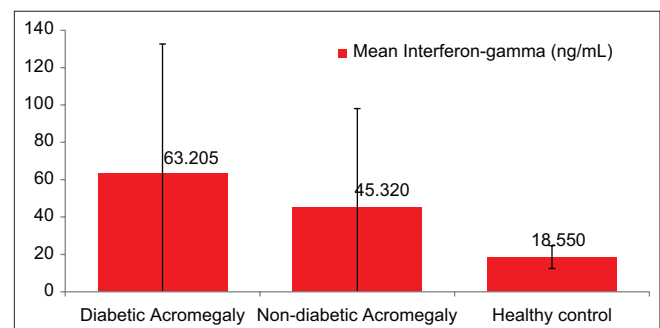


Figure 1: Interferon-gamma concentration in the diabetic acromegalic, nondiabetic acromegalic, and control groups

Table 1: Interferon-gamma concentration in diabetic acromegalic, nondiabetic acromegalic, and control groups

INF- γ (ng/mL)	Diabetic acromegaly, <i>n</i> (%)	Nondiabetic acromegaly, <i>n</i> (%)	Healthy control, <i>n</i> (%)
Low	-	-	-
Normal (1.2-80)	-	1 (2.4)	1 (2.5)
High	39 (100)	40 (97.6)	39 (97.5)
Mean $\pm$ SD (range)	63.205 $\pm$ 69.951 (18.66-315.93)	45.320 $\pm$ 52.728 (1.675-326.555)	18.550 $\pm$ 6.132 (6.468-34.149)

SD: Standard deviation, INF- γ : Interferon-gamma

Table 2: Interferon-gamma concentration in acromegalic diabetic, acromegalic nondiabetic acromegalic, and control groups according to age and gender

	INF- γ (ng/mL)					
	Diabetic acromegaly		Nondiabetic acromegaly		Healthy control	
	<i>n</i>	Mean $\pm$ SD	<i>n</i>	Mean $\pm$ SD	<i>n</i>	Mean $\pm$ SD
Age (years)						
<30	-	-	1	22.595 $\pm$	4	16.607 $\pm$ 9.941
30-39	3	36.670 $\pm$ 11.944	9	54.411 $\pm$ 47.317	7	19.588 $\pm$ 4.917
40-49	18	75.144 $\pm$ 88.111	12	32.029 $\pm$ 21.020	16	19.494 $\pm$ 5.685
50-59	10	53.569 $\pm$ 56.938	16	52.471 $\pm$ 74.165	9	17.116 $\pm$ 7.341
≥ 60	8	58.337 $\pm$ 51.684	3	40.640 $\pm$ 28.876	4	18.127 $\pm$ 4.187
<i>P</i>		0.771 [^]		0.836 [^]		0.844 [^]
Age (years)						
<50	21	69.648 $\pm$ 82.484	22	40.756 $\pm$ 34.979	27	19.090 $\pm$ 6.062
≥ 50	18	55.688 $\pm$ 53.124	19	50.603 $\pm$ 68.527	13	17.427 $\pm$ 6.368
<i>P</i>		0.542 [#]		0.558 [#]		0.429 [#]
Gender						
Male	26	74.412 $\pm$ 82.875	27	49.071 $\pm$ 62.227	20	18.732 $\pm$ 7.813
Female	13	40.790 $\pm$ 19.223	14	38.085 $\pm$ 26.919	20	18.367 $\pm$ 4.007
<i>P</i>		0.160 [#]		0.534 [#]		0.853 [#]

[#]Significant difference between two independent means using Student's *t*-test at 0.05 level, [^]Significant difference among more than two independent means using ANOVA test at 0.05 level. SD: Standard deviation, INF- γ : Interferon-gamma

Table 3: Interferon-gamma concentration in diabetic acromegalic and nondiabetic acromegalic patients according to disease duration and Gamma-Knife use

	INF- γ (ng/mL)			
	Diabetic acromegaly		Nondiabetic acromegaly	
	<i>n</i>	Mean $\pm$ SD	<i>n</i>	Mean $\pm$ SD
Duration since diagnosis (years)				
<5	13	48.046 $\pm$ 49.824	19	48.147 $\pm$ 69.000
5-9	16	66.781 $\pm$ 70.688	16	48.841 $\pm$ 38.718
≥ 10	10	77.190 $\pm$ 91.923	6	26.975 $\pm$ 11.450
<i>P</i>		0.603 [^]		0.664 [^]
Duration since diagnosis (years)				
<10	29	58.383 $\pm$ 61.892	35	48.464 $\pm$ 56.409
≥ 10	10	77.190 $\pm$ 91.923	6	26.975 $\pm$ 11.450
<i>P</i>		0.471 [#]		0.363 [#]
Gamma-Knife				
Yes	16	66.321 $\pm$ 73.885	15	44.979 $\pm$ 26.790
No	23	61.038 $\pm$ 68.685	26	45.516 $\pm$ 63.611
<i>P</i>		0.820 [#]		0.975 [#]

[#]Significant difference between two independent means using Student's *t*-test at 0.05 level, [^]Significant difference among more than two independent means using ANOVA test at 0.05 level. SD: Standard deviation, INF- γ : Interferon-gamma

DISCUSSION

Interferon-gamma is the highest in diabetic acromegalic patients, thus it was found that both diseases augment the level of INF- γ . Being acromegalic but

nondiabetic did not reduce such high INF- γ level; this may be attributed to the high cytokine levels, particularly interleukin-10.^[10,11]

However, the results are not in line with Wolters *et al.*^[12] who found that there is no significant elevation of INF- γ in acromegalic patients.

Interferon-gamma is the highest in the presence of diabetes and acromegaly followed by acromegaly then the control. The studies on INF- γ in DM are really scarce, but it has been stated that INF- γ may be a predictor of the development of foot ulcer in diabetics and correlates positively with diabetes duration.^[13]

Good glycemic control is found to be associated with higher levels of INF- γ reflecting better immune response and reducing the chance of infections.^[14]

The immune system may have an impact on the pathogenesis and progression of acromegaly as it has been found that somatostatin, GH, and IGF-1 receptors are present on thymic cells and may have a role in immune differentiation.^[15]

Male gender is associated with the higher INF- γ versus female gender in acromegalic diabetic patients followed by acromegalic nondiabetic patients, but there is no gender difference in the control group. The studies on INF- γ were reflective of its effect on atherosclerotic lesions in experimental animals as INF- γ deficiency in male mice results in progression of atherosclerotic lesions, but this is not true in female mice as INF- γ deficiency is not shown to result in any impact on atherosclerotic lesions, so the effect is strictly restricted to males.^[16]

Table 4: Interferon-gamma concentration in diabetic acromegalic, nondiabetic acromegalic, and control groups in relation to statin use and lipid profile

	INF- γ (ng/mL)					
	Diabetic acromegaly		Nondiabetic acromegaly		Healthy control	
	<i>n</i>	Mean $\pm$ SD	<i>n</i>	Mean $\pm$ SD	<i>n</i>	Mean $\pm$ SD
Statin drug						
Yes	6	35.778 $\pm$ 22.244	1	45.890 $\pm$	-	-
No	33	68.192 $\pm$ 74.609	40	45.305 $\pm$ 53.399	40	18.550 $\pm$ 6.132
<i>P</i>		0.303 [#]		0.991 [#]		
HDL (mg/dL)						
Low	25	63.152 $\pm$ 80.479	17	38.505 $\pm$ 25.291	1	23.110 $\pm$
Normal (35-70)	14	63.300 $\pm$ 48.431	24	50.147 $\pm$ 65.815	39	18.433 $\pm$ 6.166
<i>P</i>		0.995 [#]		0.493 [#]		0.458 [#]
LDL (mg/dL)						
Low	3	56.071 $\pm$ 19.447	8	34.617 $\pm$ 23.578	25	17.667 $\pm$ 5.860
Normal (65-170)	32	59.137 $\pm$ 63.647	28	50.641 $\pm$ 62.150	15	20.021 $\pm$ 6.493
High	4	101.100 $\pm$ 133.136	5	32.644 $\pm$ 11.344	-	-
<i>P</i>		0.531 [^]		0.648 [^]		0.245 [^]
VLDL (mg/dL)						
Low	39	63.205 $\pm$ 69.951	41	45.320 $\pm$ 52.728	40	18.550 $\pm$ 6.132
Normal (65-170)	-	-	-	-	-	-
<i>P</i>		-		-		-
Cholesterol (mg/dL)						
Normal (<200)	23	53.927 $\pm$ 48.314	25	39.165 $\pm$ 26.202	40	18.550 $\pm$ 6.132
High	16	76.542 $\pm$ 93.009	16	54.936 $\pm$ 78.446	-	-
<i>P</i>		0.327 [#]		0.357 [#]		-
Triglyceride (mg/dL)						
Normal (40-140)	6	124.866 $\pm$ 105.433	10	45.703 $\pm$ 30.862	31	18.197 $\pm$ 5.438
High	33	51.994 $\pm$ 56.843	31	45.196 $\pm$ 58.491	9	19.765 $\pm$ 8.381
<i>P</i>		0.017 [#]		0.979 [#]		0.506 [#]

[#]Significant difference between two independent means using Student's *t*-test at 0.05 level, [^]Significant difference among more than two independent means using ANOVA test at 0.05 level. SD: Standard deviation, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, VLDL: Very-low-density lipoprotein, INF- γ : Interferon-gamma

Overweight patients have the highest level of INF- γ among all studied patients and control, cytokines as INF- γ are known to be high in obese patients and may predict progression of the atherosclerotic lesion.^[17]

The duration of disease has its impact on INF- γ in the enrolled patients, thus longer duration of acromegaly in diabetic acromegalic patients is associated with high INF- γ , but in acromegalic nondiabetics, the reverse is true as the presence of diabetes results in progressive elevation of INF- γ years by years. Diabetes and acromegaly result in high INF- γ in statin users, thus statin may cause an increment in INF- γ in diabetic acromegalic. Statin is known to suppress INF- γ production in cell lines, and it has been postulated that statin augments the action of immunosuppressive agents in patients with organ transplantation.^[18]

HDL is found to have no impact on INF- γ level. The studies on such correlation are not available, however, the correlation between IGF-1 and HDL is found to be positive in type 2 diabetic patients.^[19]

CONCLUSION

- Interferon-gamma is high in acromegalic diabetic patients, nondiabetic acromegalic patients, and controls (100%, 97.6%, and 97.5%, respectively)
- Interferon-gamma is elevated in patients with acromegaly only in the age group of 30–39 years, but in those with diabetes, the elevation is noticed later within the age group of 40–49 years as if concomitant diabetes delays its elevation
- Interferon-gamma is high in acromegalic patients but higher when there is concomitant diabetes
- Longer duration of acromegaly is associated with higher INF- γ , and the use of Gamma-Knife radiosurgery is shown to increase INF- γ in acromegalic patients, provided that they are diabetics
- In diabetic acromegalic patients, INF- γ is found to be high in nonstatin users, but the difference from statin users is marginal.

Recommendation

A well-designed prospective study enrolled higher number of acromegalic patients is highly recommended to find out

then impact of INF- γ on the progression of acromegaly and its mortality to find out a modality of therapy that modulates the level of this molecule in the fruitful way.

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Conflicts of interest

There are no conflicts of interest.

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