

# A Mathematical Model for Regulation of Fuel Metabolism during Exercise in Hypopituitarism with Growth Hormone Deficiency

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## Abstract

In this paper we introduced a reliability model about Lomax and Gompertz distribution. Growth Hormone (GH) has a strong lipolytic action and its secretion is increased during exercise. Data on fuel metabolism and its hormonal regulation during prolonged exercise in patients with growth hormone deficiency is rare. This study aimed at evaluating the hormonal and metabolic response during aerobic exercise in GHD patients. Using these results we found Lomax distribution model is more efficient model than Gompertz model and finally we conclude that the application part is fitted with the mathematical models and conclusion is compared with medical report. This will be very useful for medical professional.

**Keywords:** Gompertz Distribution, Lomax Distribution, NHPP, GHD.

## INTRODUCTION

Software reliability is the probability that can operate without failure for a period of time at constant born environmental conditions. Thus, the reliability from the software is a central difficult during the development process of the software. The subject must be satisfied the requirements of the user and testing cost. The reliability and the cost during the development process of the software with considerations for a release time can be an indispensable problem. Many software reliability models have been accomplished so far. These

models of the software reliability using Non-Homogenous Poisson process [7] have the assumption that if a fault occurs immediately removed and no new fault has occurred during the debugging process.

In this software reliability field, the Enhanced Non-Homogenous Poisson process [ENHPP] model was presented using test coverage property [8]. In [7] proposed software reliability a model with the property of an exponential curve. The feature type of the mean value function was applied to the total number of defects have S-shaped or exponential shape form. The generalized models using a growth model of the delayed S-shaped reliability and inflection S-shaped reliability were presented. In [14],[15] proposed a software reliability changing point problem and generalized reliability growth model using changing point was presented[13].

An evaluation of software stability was presented by [12]. In conjunction with this model [10] presented an efficient technique to predict a software reliability using the testing-effort function of generalized logistic property and the parameter for change point form.

In [11] described that S-type model can be applied to the learning efficient for the software failure number and test tools. In this paper, the characteristics of Lomax and Gompertz distribution NHPP model for the software reliability were employed using a Non-Homogenous Poisson process from the faults of the infinite number.

**MATHEMATICAL MODEL AND ASSUMPTIONS**

In this section, we study the Software Reliability Infinite NHPP Model based on Lomax and Gompertz Distributions.

The mean value function  $m(t)$  and failure intensity function  $\lambda(t)$  of Lomax distribution model grounded on equations

$$m(t) = -\ln(1 - F(t)) \text{ and}$$

$$\lambda(t) = m'(t) = \frac{f(t)}{1 - F(t)} = h(t) \text{ ----- (2.1)}$$

can be stated next forms

$$\lambda(t) = \frac{f(t)}{1 - F(t)} = h(t) = \frac{\lambda}{(1 + \lambda t)} \text{ ----- (2.2)}$$

$$m(t) = -\ln(1 - F(t)) = k \ln(1 + \lambda t) \text{ ----- (2.3)}$$

Using  $m(x_n + \delta) = k \ln(1 + \lambda(\delta + x_n))$  and

$m(x_n) = k \ln(1 + \lambda x_n)$ , the reliability can be estimated using the next form

$$\hat{R}\left(\frac{\delta}{x_n}\right) = \exp\{-[m(\delta + x_n) - m(x_n)]\} \text{ ----- (2.4)}$$

Note that  $m(x_n + \delta)$  and  $m(x_n)$  are the mean value time for the work time  $\delta$  and  $x_n$  is the failure last time.

Also the mean value function  $m(t)$  and failure intensity function  $\lambda(t)$  for Gompertz software reliability distribution model grounded on equations

$$f\left(\frac{t}{\alpha}, \beta\right) = \alpha\beta e^{\beta t} e^{-\alpha} \exp(-\alpha e^{\beta t}) \text{ and}$$

$$F\left(\frac{t}{\alpha}, \beta\right) = 1 - \exp(-\alpha(e^{\beta t} - 1)) \text{ ----- (2.5)}$$

can be obtained next equations

$$\lambda(t) = \frac{f(t)}{1 - F(t)} = h(t) = \alpha\beta e^{\beta t} \text{ ----- (2.6)}$$

$$m(t) = -\ln(1 - F(t)) = \alpha(e^{\beta t} - 1) \text{ ----- (2.7)}$$

similarly using  $m(x_n + \delta) = \alpha\{e^{\beta(\delta+x_n)} - 1\}$  and

$m(x_n) = \alpha\{e^{\beta x_n} - 1\}$ , the reliability can be estimated as follows

$$\hat{R}\left(\frac{\delta}{x_n}\right) = \exp\{-[m(\delta + x_n) - m(x_n)]\} \text{ ----- (2.8)}$$

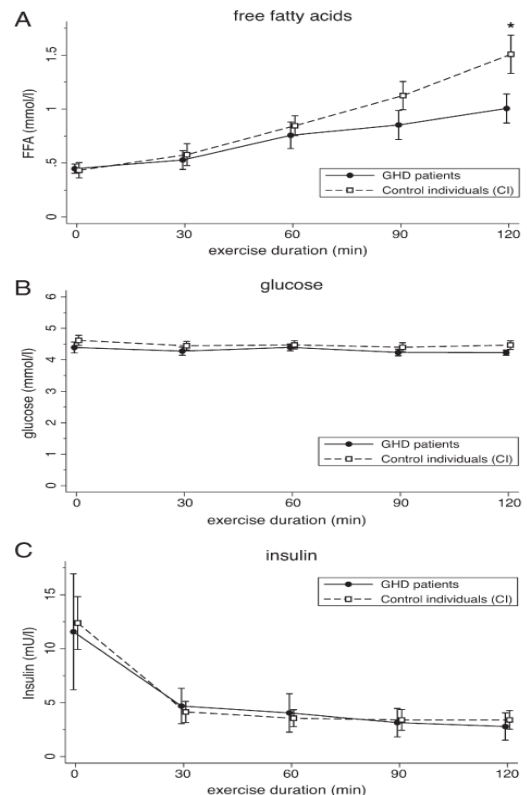
Note that  $m(x_n + \delta)$  and  $m(x_n)$  are the mean value time for the mission time  $\delta$  and  $x_n$  is the failure last time.

**APPLICATIONS**

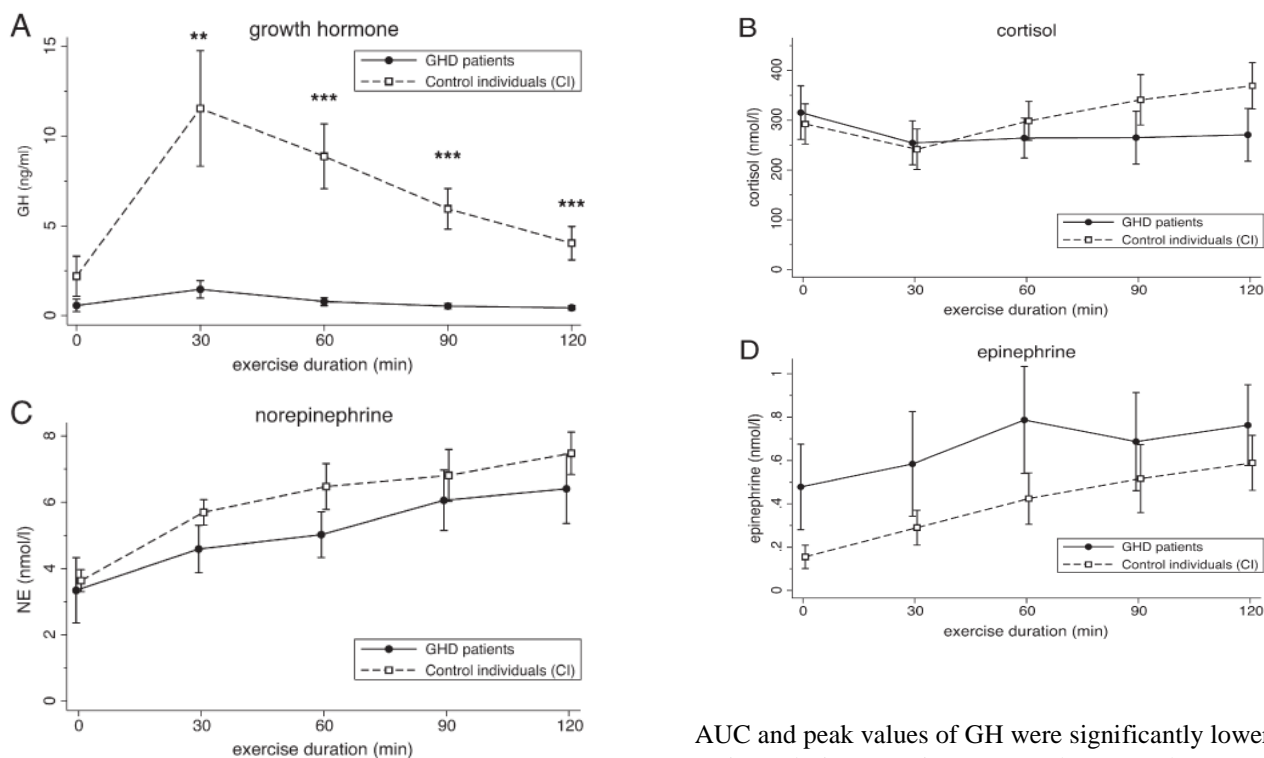
Hypopituitary patients with growth hormone deficiency (GHD) tend to have a reduced aerobic exercise capacity compared with sedentary control subjects [2]

It is established that the lack of growth hormone (GH) is accompanied by a decreased lean body mass [4] and reduced performance of the cardiovascular system [2,3]. Moreover GHD impairs the oxygen transport capacity [3]. All these factors may contribute to a reduced exercise capacity.

In healthy subjects exercise induces a strong GH secretion. In patients suffering from GHD such an exercise induced GH-response is lacking. Since GH is known to have a strong lipolytic effect we speculate that lipolysis may also be reduced during exercise in patients with GHD compared to healthy individuals. This effect could either be compensated by an increased secretion of alternative lipolytic hormones or by changes in fuel metabolism towards an increased oxidation of carbohydrates. We, therefore, aimed at investigating the hormonal and metabolic response during exercise in GHD patients compared to matched control subject. We hypothesized that a decreased availability of free fatty acids (FFA) and possibly a reduced fat oxidation during exercise may contribute to the reduced exercise capacity in patients with GHD.



**Figure 1:** Mean  $\pm$ S.E.M concentrations of the free fatty acids(panel A);glucose (panel B) and insulin(panel C) during the exercise for GHD patients(black circles with solid lines).p value for difference between GHD and CI < 0.05.



**Figure 2:** Mean  $\pm$ S.E.M concentrations of GH (panel A) cortisol (panel B), norepinephrine (panel C) and epinephrine (panel D) during the exercise for GHD patients (black circles with solid lines) and control individuals (white squares with dashed lines) p value for difference between GHD and CI < 0.01 p value for difference between GHD and CI < 0.001.

## HORMONE

In GHD GH values showed a slight but significant increase after 30 min ( $1.46 \pm 1.55$  ng/ml) and 60 min ( $0.78 \pm 0.71$  ng/ml) of exercise (p compared to baseline b0.001 and b0.05 at 30 and 60 min, respectively). Fig 3.2 (A). As depicted in Fig 3.2 (B), cortisol values tended to drop slightly in GHD patients after 30 min and remained stable for the rest of the exercise (ANOVA p = 0.72). Furthermore epinephrine and NE showed a significant increase during exercise in patients suffering from GHD (Friedman test p-value for Adrenalin = 0.015 and for NA b 0.001, respectively). Fig 2 (c & D). Insulin level significantly decreased during exercise in GHD patients (Friedman Test p b 0.001).

In CI there was a significant and transient increase of GH with highest values after 30 min ( $11.55 \pm 10.16$  ng/ml, p compared to baseline b 0.01) and a continuous decline during the following 90 minutes of exercise Fig 2 (A).. In CI cortisol values tended to slightly drop after 30 minutes and then raised again during the rest of exercise ANOVA p = 0.13) Fig 2 (B).. Epinephrine and NE showed a significant increase in CI throughout the entire exercise (p b 0.001 for Epinephrine and NE) with highest values at 120 min of exercise. Fig 2 (C & D).

AUC and peak values of GH were significantly lower in GHD patients during exercise compared to CI (p b 0.001 for AUC- and peak-GH). AUC cortisol and peak cortisol were similar in GHD and CI (p for AUC cortisol = 0.44, p for peak cortisol = 0.40). When comparing the incremental AUCs of cortisol there was a trend towards higher cortisol values in CI compared to GHD (incremental AUC-cortisol  $11,199 \pm 8214$  vs.  $8507 \pm 10,045$  mmol \* min/l, p = 0.059). AUC and peak concentrations of catecholamine's and insulin did not significantly differ between GHD patients and CI.

## DISCUSSION

The main findings can be summarized as follows: First, there was a reduced exercise capacity in GHD patients compared to CI. Second, during a standardized aerobic exercise of 120 minutes duration FFA levels increased in both groups but peak FFA values were significantly lower in GHD patients compared to CI, whereas glucose availability was similar in GHD compared to CI. Third, patients with GHD had a higher RER and a lower fat oxidation compared to CI at the end of the 120-minute exercise. Fourth, lipolytic hormones such as catecholamine's and cortisol do not completely compensate for the lack of lipolytic action of GH in patients with GHD during exercise.

A reduced exercise capacity based on  $VO_{2max}$  measurement in patients with GHD is consistent with previous studies [2]. Besides a possible metabolic factor there are several possible factors that may contribute to this finding: GHD is characterized by a reduced lean body mass [9], impaired cardiac function, namely alterations in preload and after load [1], an elevated peripheral vascular resistance, pointing towards a negative effects of GHD on the performance of the

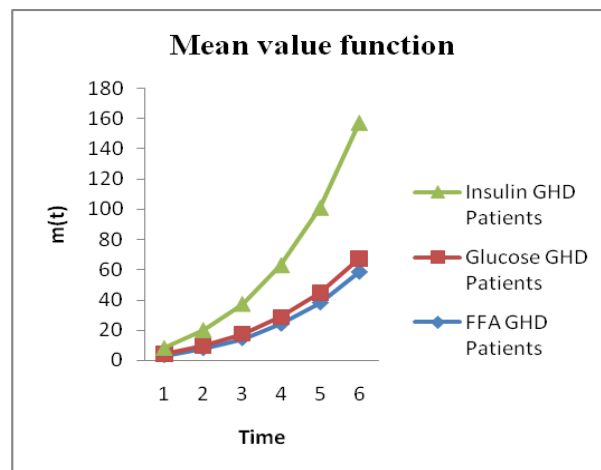
cardiovascular system. This hypothesis is further supported by the presence of GH and IGF-1 receptors in myocardium and blood vessels [5], which makes a direct effect of GH and IGF-1 in the heart muscle and cardiac and cardiovascular function likely. Additionally, GHD impairs the oxygen transport capacity, mainly by a reduced erythropoietin. It is established that in healthy individuals physical exercise results in an increase in GH secretion which, in turn, induces lipolysis, as evidenced by an increase in FFA concentrations, as documented in the present study and in present work. However, in patients with GHD Kanaley et al. Have shown that administration of GH during exercise leads to a marked increase in FFA as well as FFA fluxes in keeping with our findings and further supporting the importance of the lipolytic action of GH during exercise. In contrast, GH withdrawal decreases fat turnover during exercise, which may contribute to a reduced exercise capacity in GHD [12]. Since adipose tissue biopsy was not part of the present study we can only speculate on GH mediated differences in triacylglycerol lipase activity.

The differences in the serum FFA concentrations between GHD and CI were most pronounced at the end of the 2h exercise period suggesting that the other lipolytic hormones such as catecholamines and cortisol were sufficient to increase FFA availability at the beginning of the 2h exercise. Interestingly, these findings were paralleled by a significantly higher fat oxidation in CI compared to GHD patients at the end of exercise, indicating that there is not only an impaired availability of FFA during exercise in GHD patients but the lack of GH may also negatively impact on FFA uptake and intracellular trafficking of FFA towards the mitochondria including oxidation. Based on these results it is possible that besides the well known factors such as reduced lean body mass, oxygen transport capacity and negative effect of GHD on the performance of the cardiovascular system metabolic factors, in particular FFA availability, uptake and oxidation may contribute to the reduced exercise capacity seen in patients with GHD [12]. Furthermore high-dose GH increases lipolysis and FFA availability at rest, during and after over 3-12 months was shown to improve aerobic exercise capacity and muscle mass.

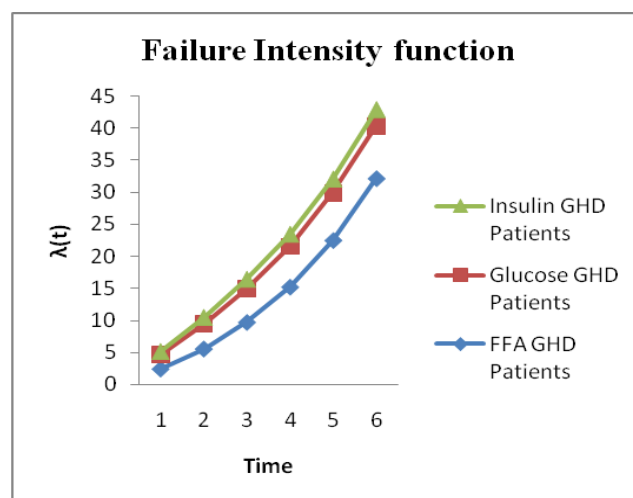
An increase in catecholamine's, cortisol and GH, as well as reduced in insulin secretion are well known hormonal responses to exercise in healthy individuals [4] and were also observed in the resent study. Besides the reduced GH secretion and a flattered cortisol response we found similar hormonal secretion patterns during the exercise also for the GHD patients. The flattened cortisol profile can be explained by the fact that five of the ten GHD patients additionally suffered from hypothalamo pituitary adrenal axis insufficiently and were, therefore, substituted with hydrocortisone as appropriate before the exercise. We cannot exclude a certain influence of the flattened cortisol profile on lipolysis and fat utilization in the GHD group, since cortisol

increases on one hand lipolysis [6] and on the other hand intravascular triglyceride degradation by activating lipoprotein lipase. Nevertheless AUC and peak values of cortisol in GHD and CI during exercise were not statistically different, which makes a major influence of the substituted cortisol deficiency unlikely. Of interest the blunted GH response in GHD patients during exercise was neither compensated by an increased catecholamine nor by a reduced insulin secretion compared to CI.

## MATHEMATICAL RESULTS

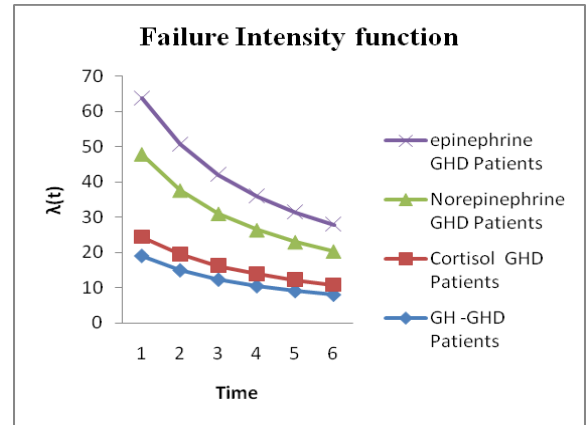
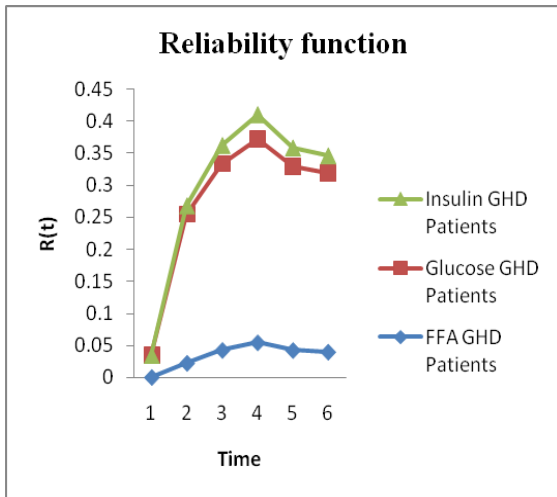


The plot of probability mean value function of insulin GHD patients' dose shows its superiority than the functions glucose GHD patients' dose and GHD patients' control. The plot of insulin GHD patients' dose function initially monotonically increasing up to  $t=7$  h and then decreasing monotonically. The rate of decreasing is comparatively good than glucose GHD patients' dose and control functions. After injecting FFA GHD dose to patients, growth hormone levels are suppressed as time goes on.



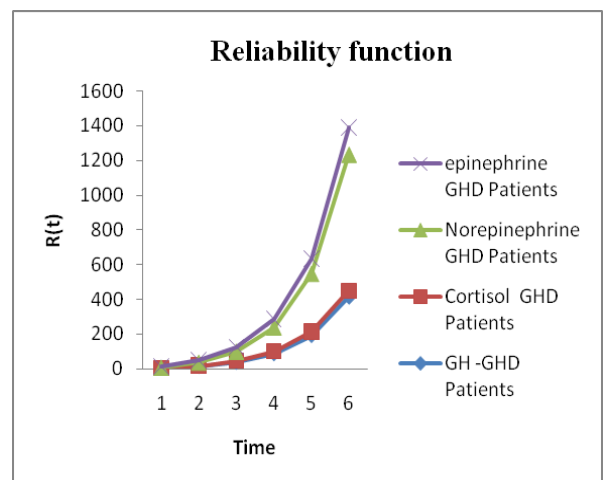
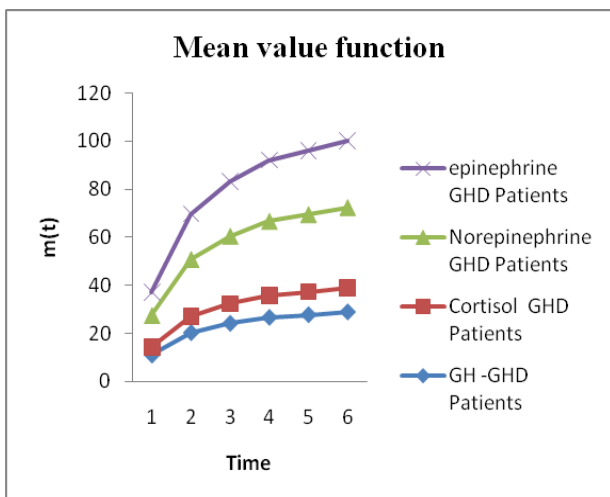
The plot of Failure intensity function of insulin GHD patients' dose dominates the glucose GHD patients' dose and control Failure intensity function in the specified range. The probability Failure intensity function of insulin GHD patients' dose decreases rapidly than glucose GHD patients' dose and control functions. The Failure intensity function of insulin GHD patients' levels when injected insulin GHD patients' beyond any given specified time is higher than the other two cases of glucose GHD patients' dose and control.

The plot of probability mean value function of Epinephrine GHD patients, Norepinephrine GHD patients' dose shows its superiority than the functions Cortisol GHD patients' dose and GH-GHD patients' control. The plot of Epinephrine GHD patients' dose function initially monotonically increasing up to  $t=6$  h and then decreasing monotonically. The rate of decreasing is comparatively good than Epinephrine GHD patients' dose and control functions. After injecting GH-GHD patients, growth hormone levels are suppressed as time goes on.



The reliability function of insulin GHD patient's dose function is extremely good than the reliability function of glucose GHD patients' dose and control functions. According to plots the functions, the reliability function of insulin GHD patient's dose, FFA GHD patients and control functions are 4.5, 4.2, and 1.9 respectively. The reliability function is also known as failure rate. The failure rate of development of insulin GHD patient's dose is high when injecting glucose GHD patients' dose comparing with the injecting glucose GHD patients' dose and control.

The plot of Failure intensity function of Epinephrine GHD patient's GHD patients' dose dominates the Nor epinephrine GHD patients' dose and control Failure intensity function in the specified range. The probability Failure intensity function of Epinephrine GHD patients' dose decreases rapidly than Nor epinephrine GHD patients' dose and control functions. The Failure intensity function of Epinephrine GHD patients' levels when injected insulin GHD patients' beyond any given specified time is higher than the other two cases of Nor epinephrine GHD patients, Cortisol GH-GHD patients and control.



The reliability function of Epinephrine GHD patient's dose function is extremely good than the reliability function of Nor epinephrine GHD patients' dose and control functions. According to plots the functions, the reliability function of Epinephrine GHD patient's dose, GH -GHD patients and control functions are 4.5, 4.2, and 1.9 respectively. The reliability function is also known as failure rate. The failure rate of development of Epinephrine GHD patient's dose is high when injecting Nor epinephrine GHD patients' dose comparing with the injecting Cortisol GHD patients dose and control.

## CONCLUSION

In the present study, we introduced a reliability model about Lomax and Gompertz distribution. The findings of this study suggest that reduced FFA availability, uptake and oxidation may contribute to the observed reduced exercise capacity in GHD patients. Other lipolytic hormones such as catecholamines do not compensate the metabolic role of GH during exercise in GHD patients. Using these results we found Lomax distribution model is more efficient model than Gompertz model and finally we conclude that the application part is fitted with the mathematical models and conclusion is compared with medical report. This will be very useful for medical professional.

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