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A Stochastic Process Degradation Model for effects of 3-Year GH Replacement Therapy for GH Deficiency on Bone Mineral Density in Younger and Elderly Adults

S.Lakshmi [*] and A. Manickam[**]

[*] Principal Govt. Arts and Science College, Peravurani-614804. Thanjavur (Dt)., Tamilnadu, India.

E.mail id: lakshmi291082@yahoo.co.in

[**] Assistant Prof.of Mathematics, Anjalai Ammal-Mahalingam Engineering College, Kovilvenni – 614 403 Thiruvarur Dist.,Tamilnadu, India.

E.mail id: manickammaths2011@gmail.com

Abstract

The paper presents a stochastic gamma process model to account for both population (i.e sampling) and temporal variability associated with a degradation process that typically increases the probability of failure with the aging of a structure. The proposed method is more versatile than the random-variable degradation rate model commonly used in the structural reliability literature. The reason being that the random rate model cannot capture temporal variability associated with evolution of degradation. The paper also describes two methods for estimating parameters of the gamma process to facilitate its practical engineering applications. Little is known of the effects of long – term GH replacement on bone mineral content (BMC) and bone mineral density (BMD) in elderly GH –deficient (GHD) adults using Stochastic Degradation model. This study shows that GH replacement increases lumbar (L2 – L4) spine and femur neck BMD and BMC not only in younger but also in elderly GHD patients. So Mathematical result supports the notion that long – term GH replacement is also useful in elderly GHD patients.

Keywords: GH; GHD; BMD; BMC.

Mathematics subject classification: 60 G_{xx}, 62H_{xx}, 62$P_{xx.}$

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1. INTRODUCTION

The condition assessment of a structure reveals its current state in relation to the structure's resistance to applied load effects. Due to aging-related deterioration, the current condition of a structure tends to be different from the original design and construction. A key issue, however, in palling future rehabilitation is to predict the trend of future degradation of resistance. The evolution of degradation tends to be uncertain in most engineering structures due to variability associated with degradation processes is the main objective of the paper. Because deterioration is uncertain over time, it should ideally be represented as stochastic process. At first glance, it seems possible to represent the temporal variability in a deterioration process by the Brownian motion with drift. A characteristic feature of this stochastic process, however, is that a structure's resistance alternately increases and decreases. For this reason, the Brownian motion is inadequate in modeling deterioration which is monotone. In order to model monotonic progression of a deterioration process, the paper proposes a stochastic gamma process model for the resistance of a structural component. The gamma process is a stochastic process with independent, non-negative increments having a gamma distribution with identical scale parameter and a time-dependent shape parameter. The paper presents a time-independent reliability analysis method based on gamma processes, describes statistical estimation methods and highlights the advantages of the proposed method over the conventional approach.

2. RANDOM – VARIABLE DEGRADATION MODEL

The time-dependent reliability analysis typically involves degradation model for the resistance as

$$R(t) = R_0 - At^b \quad \textbf{(1)}$$

Where R_0 is the initial resistance, A is the random rate of degradation, t is the age of the component, and b reflects a non linear trend of the degradation law. The randomisation of the degradation rate reflects its variability in a large population of similar components (in a similar manner as the variability in lifetimes).If we define failure of a component as the down-crossing of resistance below an applied stress S,the failure –limit state can be written as R(t) – S = 0.The lifetime distribution can then be simply obtained from the relation

$$t = \left[\frac{R_0 - S}{A}\right]^{1/b} \quad \textbf{(2)}$$

The life time distribution can be derived in an analytical or numerical sense depending on the probability distribution of R_0 , S and A.As an illustration, consider the initial resistance and stress to be deterministic variables denoted by r_0 and s,and linear degradation law (b=1) with rate A as a gamma distributed random variable.Under these assumptions the lifetime distribution is an inverted gamma distribution. Another example is a lognormal distribution for A as used by Mori & Ellingwood (1994).Although the degradation model in Equation (1) can be considered as a stochastic process in a technical sense, the sample paths of the degradation of a component remain fixed(e.g., linear in case of b=1).Over its entire lifetime. Furthermore, the single inspection can also determine the remaining lifetime of the component without any uncertainty. In principle, if there are n unknowns in the degradation law, n number of inspections will determine the remaining lifetime of a component. The Random-Variable Degradation (RVD) model is implicit in several studies that apply the First – Order Reliability Method (FORM) for time-dependent reliability analysis. In the condition assessment and rehabilitation planning of existing structures, the uncertainty associated with the evolution of degradation over time is an important consideration for the optimisation of inspection and maintenance programs. Since the RVD model is not adequate to model temporal variability associated with degradation, we present a more formal Stochastic-Process Degradation (SPD) model to overcome this limitation. The proposed model is based on the theory of gamma processes as described in the next Section.

3. STOCHASTIC – PROCESS DEGRADATION MODEL

A difficulty in modelling time – dependent reliability is that the process of deterioration is uncertain over the life of a structure. In structural engineering, a distinction is made between a structure's resistance (e.g the crest –level of a dike) and its applied stress (e.g the water level to be withstood).A failure may then be defined as the event in which the deteriorating resistance drops below the stress. Maintenance management mainly deals with condition failure rather than structural failure (collapses).The uncertain deterioration can be regarded as stochastic processes, and the associated uncertainly can be represented by the normal distribution. This probability distribution has been used for modelling the exchange-value of shares and the movement of small particles in fluids and air. A characteristics features of this model, also denoted by the Brownian motion with drift (Karlin and Taylor 1975,chapter 7),is that a structures resistance alternately increases and decreases, like the exchange value of share, For this reason, the Brownian motion is inadequate in modelling deterioration which is monotone. For example, a dike of which the height is subject to a Brownian deterioration can, according to the model, spontaneously rise up, which of course cannot occur in pratice.In order to incorporate a monotonic increase in deterioration with age, we propose the gamma process as an ideal alternative(van Noortwijk et.al.1997).The gamma process is a stochastic process with independent, on-negative increments(e.g the increments of crest level decline of a dike)having a gamma distribution with an identical scale parameter. It implies that in case of gamma deterioration, dikes can only decrease in height due to crest-level decline. As far as the authors know, Abel-Hammed (1975) as the first to propose the gamma process as a proper model for deterioration occurring ran dome in time. In this two-page paper he called this stochastic processes the "gamma wear processes". Advantages of modelling deterioration processes through a gamma processes is that the required mathematical calculations are relatively straightforward. The gamma processes is suitable to model gradual damage monotonically accumulating over time, such

as wear,fatigue,corrosion,crack growth,erosion,consumption,creep,swell,degrading health index,et cetera.Other examples of the application of gamma processes are the theory of water storage by dams (Moran 1959,chapter 4) and the theory of risk of ruin due to aggregate insurance claims (Dufresne et.al.1991).It should be noted,however,that dam storage and risk ruin models are inherently different from stress-strength models. The mathematical definition of the gamma processes is given as follows. Recall that a random quantity X has a gamma distribution with shape parameter v > 0 and scale parameter u>0 if its Probability density function is given by

Ga(x \v,u) = $\frac{u^v}{\Gamma(v)} x^{v-1} exp\{-ux\} I_{(0,\infty)}(x)$, where $I_A(x) = 1$ for x ∈ A and $I_A(x) = 0$ for x ∉ A. and $\Gamma a = \int_{t=0}^{\infty} t^{a-1} e^{-t}\ dt$ is the gamma function for $a > 0$.Furthermore,let v(t) be a non-decreasing, right continuous, real-valued function for t ≥ 0,with v(0) ≡0.The gamma process with shape function v(t) > 0 and scale parameter u > 0 is a continuous – time stochastic process $\{X(t), t \geq 0\}$ with the following properties:

1.X(0) = 0 with probability one;

2. X(τ) – X(t) ~ Ga(v(τ)- v(t),u) for all τ > t ≥ 0;

3. X(t) has independent increments.

Let X(t) denote the deterioration at time t, t ≥ 0 ,and let the probability density function of X(t),in accordance with the definition of the gamma process,be given by

$$f_{X(t)}(x) = Ga(x/v(t), t) \quad \textbf{(3)}$$

with E(X (t)) = $\frac{v(t)}{u}$ Var (X (t)) = $\frac{v(t)}{u^2}$ **(4)**

A component is said to fail when its deteriorating resistance, denoted by R (t) = $r_0 - X(t)$,drops below the stress s.We assume both the initial resistance r_0 and the stress s to be deterministic. Let the time at which failure occurs be denoted by the life time T. Due to the gamma distributed Deterioration, Equation (3),the lifetime distribution can then be written as:

$$F(t) = Pr\{T \leq t\} = Pr\{X(t) \geq r_0 - s\} = \int_{x=r_0-s}^{\infty} f_{X(t)}(x)dx = \frac{\Gamma(v(t),[r_0 - s\,]u)}{\Gamma(v(t))} \quad \textbf{(5)}$$

Where$\Gamma(a,x) = \int_{t=x}^{\infty} t^{a-1} e^{-t}\ dt$ is the incomplete gamma function for x ≥ 0 and

$a > 0$.Using the chain rule for differentiation, the probability density function of the life time is

$$f(t) = \frac{\partial}{\partial t}\left[\frac{\Gamma(v(t),[r_0 - s\,]u)}{\Gamma(v(t))}\right] = \frac{\partial}{\partial \tilde{v}}\left[\frac{\Gamma(\tilde{v},[r_0 - s\,]u)}{\Gamma(\tilde{v})}\right]_{\tilde{v}=v(t)} v'(t) \quad \textbf{(6)}$$

Under the assumption that the shape function $v(t)$ is differentiable. The partial derivative in Equation (6) can be calculated by the algorithm of Moore (1982).Using a series expansion and a continued fraction expansion, this algorithm computes the first and second partial derivatives with respect to x and a of the incomplete gamma integral

$$P(a,x) = \frac{1}{\Gamma(a)} \int_{t=0}^{x} t^{a-1} e^{-t}\ dt = \frac{\Gamma(a) - \Gamma(a,x)}{\Gamma(a)}.$$

Under the assumption of modelling the temporal variability in the deterioration in terms of a gamma process, the question which remains to be answered is how its expected deterioration increases over time. Empirical studies show that the expected deterioration at time t is often proportional to a power law:

$$v(t) = ct^b \quad \textbf{(7)}$$

For some physical constants c > 0 and b > 0.Some examples of expected deterioration according to a power law are the expected degradation of concrete due to corrosion of reinforcement (linear b = 1 ;Ellingwood & Mori (1993),sulfate attack(parabolic b=2; Ellingwood & Mori (1993)),diffusion – controlled aging (square root:b =0.5; Ellingwood & Mori (1993),and creep (b =1/8; Cinlar et.al.(1977)) and the expected scour-hole depth (b=0.4;Hoffmans & Pilarczyk(1995) and van Noortwijk & Jlatter (1999)).Because there is often engineering knowledge available about the shape of the expected deterioration in terms of the parameter b in Equation (7),this parameter may be assumed constant. In the event of expected deterioration in terms of a power law, the parameters c and u yet must be assessed by using expert judgment and/ or statistics. It should be noted that the gamma processes is not restricted to using a power law for modelling the expected deterioration over time. As a matter of fact, any shape function $v(t)$ suffices, as long as it is non-decreasing, right continous,and real valued function. The main difference between the SPD model and the RVD model is that the sample of the former approach are discontinuous and monotone, whereas the sample paths of the latter approach are straight lines (for a linear degradation law).According to the gamma processs,one inspection thus reveals only one observed increment which can be used to predict future deterioration. According to the random –variable degradation model,however,one inspection already exists the future deterioration beforehand .Although the RVD model can be very well used as an approximation, one should be careful as soon as inspections are involved, For inspection models based on the gamma process, see e.g. van Noortwijk et al.(1995,1997).

4. APPLICATION

GH deficiency (GHD) in hypo pituitary adults results in multiple abnormalities in terms of body composition, bone mass,

and glucose and lipid metabolism[4,8,9].GH replacement normalizes most of these abnormalities in adult populations including patients of various ages[4,8,9].The response to GH replacement may however, vary in different subgroups of patients depending on the cause and severity of disease[4,8,9] as well as on whether the disease was acquired in childhood or adulthood[1,18].GH secretion declines with increasing age [5,20],but there are distinct differences between normal elderly subjects and elderly adults with structural hypothalamic-pituitary disease. The elderly GH adults have lower GH secretion[26] and increased total body fat [25] compared with age-matched healthy subjects, whereas there is little difference in terms of lean mass[25].The results of several studies suggest that GH replacement in elderly GHD patients has approximately similar efficacy as that in younger GHD adults in terms of quality of life, body composition, and serum lipid pattern [11,12,16,21].Young GHD adults have reduced bone mineral content (BMC) and bone mineral density(BMD)[24]. Short-term(≤12months)GH replacement in relatively young GHD adults results in unchanged or even decreased bone mass[4,8,24],whereas long-term GH replacement improves BMC and BMD in open studies [4,8,9,15,17,24].Meta-analyses, mainly of randomized GH treatment trials with relatively short duration, have shown either a moderate increase in lumbar spine BMD,which could have been due to relatively small sample size . In elderly GHD adults not receiving GH replacement, bone mass and density are approximately similar to that in healthy age-matched controls [12,13].Little is known whether GH replacement affects BMC and BMD in elderly GHD adults. The effect of 3-year GH replacement on bone mass and density was determined in 45 GHD patients > 65 years at the beginning of study and in 45 matched younger control GHD patients. All the patients had adult-onset GHD.

4.1 Results

The elderly GHD patients and the younger control GHD patients were comparable in terms of gender, body height, body weight, BMI, waist circumference, waist: hip ratio, and the number of anterior pituitary hormonal deficiencies. The elderly patients had, however, longer duration of hypopituitarism compared with the younger patients.

4.2 GH dose and serum IGF-I

The daily dose of GH was increased during the first year of treatment and was then slightly reduced during the last year of GH replacement. At all time points of the study, the dose of GH was higher in the younger patients than in the elderly patients. Serum IGF-I levels increased during the first year of the study and then decreased slightly during the last year. The elderly patients had lower absolute level of serum IGF-I concentration than the younger patients, but there was no between group difference in the treatment response. Mean IGF-I SDS (adjustment for age and gender) was similar in both groups at all time points and was within the normal range (±2 S.D) in both study groups.

4.3 Bone mineral content

At baseline, no difference in total body and lumbar (L2-L4) spine BMC were seen between the groups, whereas femur neck BMC was lower in the elderly compared with the younger GHD patients ($P < 0.05$). After 3 years of GH replacement, total body BMC had increased only in the younger patients, but there was no statistically significant difference in responsiveness between groups. Lumbar (L2-L4) spine BMC increased to a similar extent in both study groups. The increase in femur neck BMC was more marked in the younger patients ($P <0.05$ vs elderly group).At the end of study, femur neck BMC was still lower in the elderly patients ($P<0.05$).

4.4 Bone mineral density.

Total body, lumbar (L2-L4) spine, and femur neck BMD are shown in the Figs 1,2,3.At baseline, femur neck BMD and t-score were lower in the elderly GHD patients($P<0.001$ vs. younger GHD controls)while total body BMD and lumbar (L2-L4) spine BMD were similar in both groups. The elderly patients had,however,a higher mean lumbar (L2-L4) spine z-score than the younger patients at baseline ($P<0.05$).At baseline, the z-score values were ~0(predicted base on age and gender) in the elderly GHD group.There was no difference between groups in the response to 3 – year GH replacement in terms of BMD at all skeletal sites measured. After 3 years, total body BMD was unchanged, whereas lumbar (L2-L4) spine BMD and femur neck BMD had increased within both study groups. At the end of study, femur neck BMD and t-score were still lower and lumbar (L2-L4) spine z-score was still higher in the elderly GHD patients compared with elderly GHD controls ($P<0.001$,$P<0.001$, and $P<0.05$ respectively).

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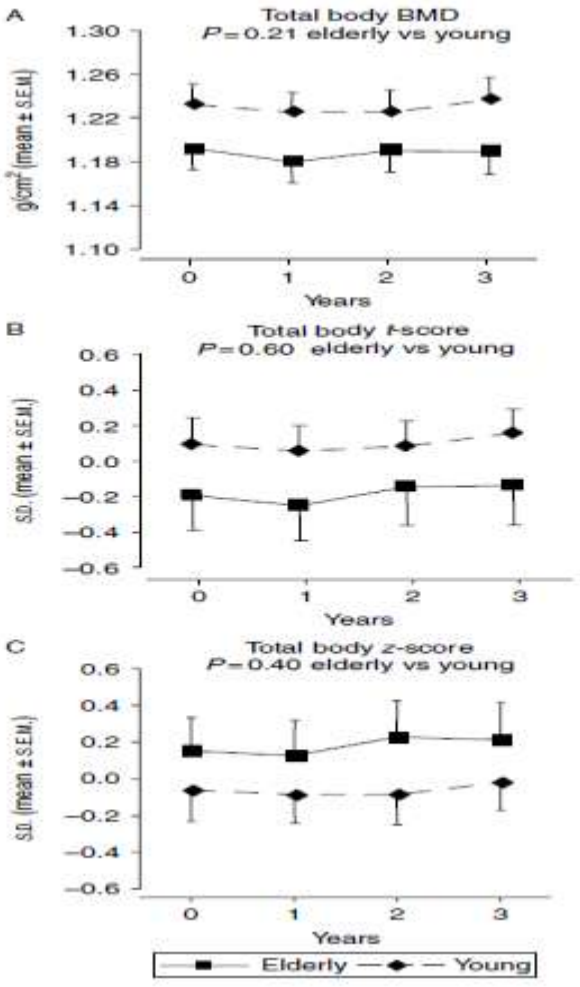

Figure:1(A) Total body(A) BMD,(B) t-score and (C) z-score during 3 –year GH replacement in 45 GH adults > 65 years and 45 younger control GHD adults The vertical bars indicate the S.E.M for the mean values shown.There were no within- or between-group differences in terms of total body BMD,t –score, or z-score .

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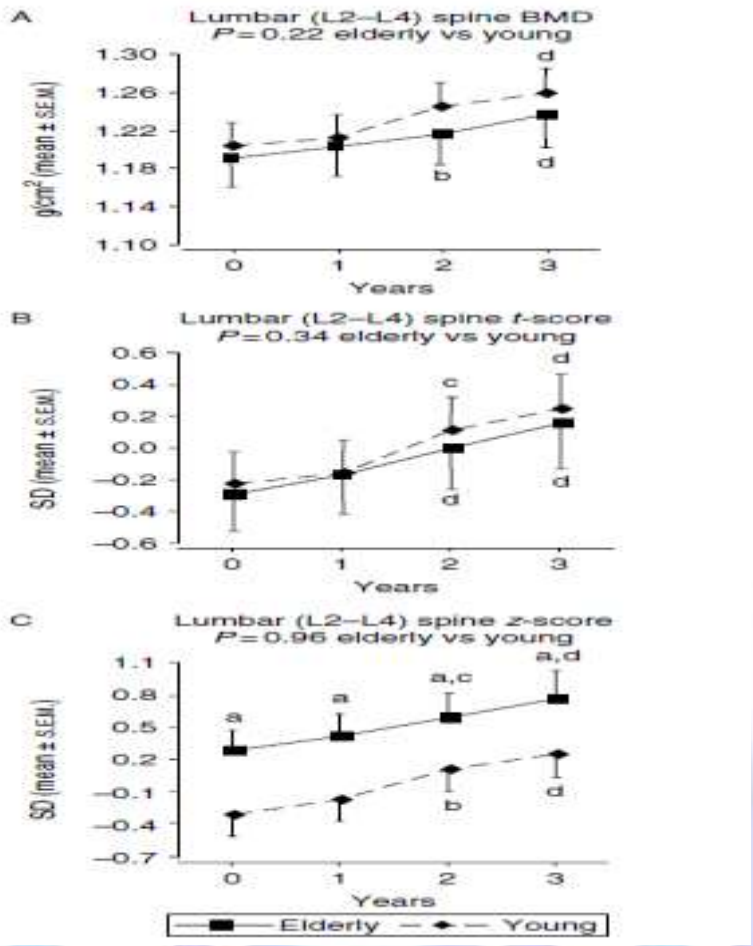

Figure:1(B) Lumbar (L2 – L4) spine BMD,(B) t-score and (C)z-score during 3-year GH replacement in 45 GHD adults > 65years and 45 younger control GHD adults. The vertical bars indicate the S.E.M for the mean vales shown. Between - group P values (0-3 years) are based on an analysis of th percentage or change from baseline,whereas other P values are based on an analysis of the absolutevalues $a_P < 0.05$ vs ;younger patients $b_P < 0.05$vsbaseline;$c_P < 0.01$ vs baselin $d_P<0.001$ vs baseline.

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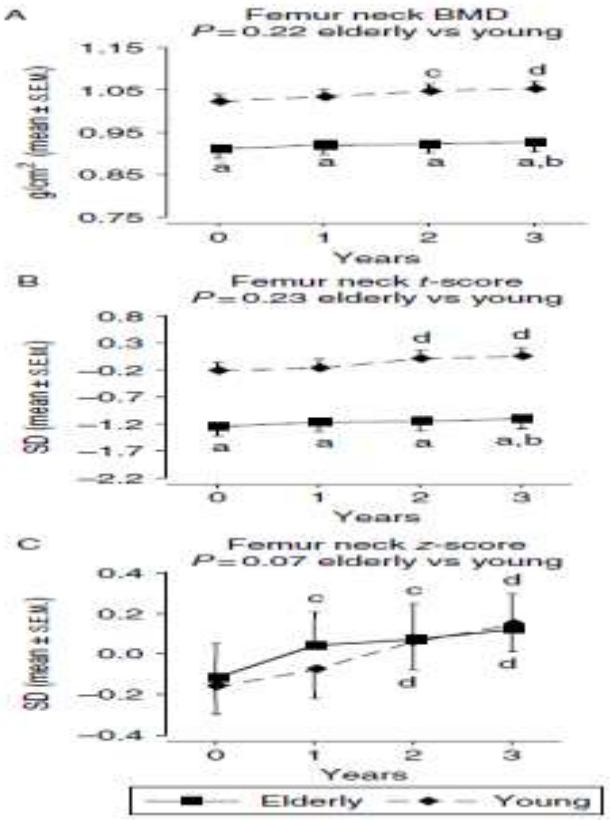

Figure: 1(C) Femur neck (A) BMD (B) t-score and (C) z-score during 3 –year GH replacement in 45 GHD adults > 65 years and 45 Younger control GHD adults. The vertical bars indicate the S.E.M for mean values shown. Between-group P values (0-3 years) are based on an analysis of the percent change or change from baseline, whereas other P values are base on an analysis of the absolute values, a $_P$<0.001 vs;b $_P$<0.05vs baseline;c$_P$<0.01 vs. Baseline d $_P$<0.001 vs baseline.

5. DISCUSSION

The first study that has explored the long- term effects of GH replacement on bone mass and density specifically in elderly GHD adults. The 3-year GH replacement in patients > 65 years with adult-onset GHD improved body composition and increased lumbar (L2-L4) spine and femur neck BMC and BMD.A limitation of this study is that there was no untreated control group. However; we compared the effect of the 3-year GH replacement in elderly GHD patients with that in younger GHD adults. The use of t-scores and z-scores may also, to some extent, compensate for the lack of an untreated control group. Two patients in each group started GH replacement with a fixed dose of GH based on body weight that was gradually lowered and individualized .In the remaining patients, the dose of GH was individualized from the beginning of the study. In line with some previous observations [12,14], this individualized GH replacement resulted in a lower dose of GH in the elderly GHD patients than in the younger GHD patients [12,14].The 3-year GH replacement resulted in a mean IGF-I SDS within the normal physiological range (±2 S.D) in both groups. However, the mean IGF-I SDSs were in the upper normal range (between +1 and +2 S.D of predicted values)after 2 years of GH replacement, and in both groups, the dose of GH was slightly reduced during the last year of the study. Furthermore, although the younger patients tended to have more marked increases in serum IGF-I concentration and IGF-I SDS than the elderly patients, there were no statistical difference between groups. This supports that elderly GHD patients are sensitive to GH and that a relatively low dose of GH can produced a significant increase in serum IGF-I concentration in this group of patients. The 3-year GH replacement improved body composition in both study groups. There were sustained reductions in waist circumference, waist: hip ratio and total body fat without any between- group difference.LST was increased throughout the 3-year GH replacement in both groups. In line with this, several previous studies have demonstrated that GH replacement has approximately similar efficacy in terms of improvement of body composition in younger and elderly GHD patients[12,16,21].There was no between –group difference at baseline or in response to the 3-year GH replacement in total body and lumbar (L2-L4) spine BMC.The elderly patients had lower femur neck BMC than the younger control GHD patients at baseline and the younger patients had more marked increase in femur neck BMC in response to treatment.However,after correction for the longer duration of hypopituitarism in the elderly patients using analysis of covariance, femur neck BMC did no longer differ between groups.Moreover,the more marked increase in femur neck BMC in the younger patients lost statistical significance when correcting for the higher dose of GH in the younger patients. Taken together, these findings indicate that BMC is approximately similar in elderly and younger GHD patients and that there is no major difference in responsiveness to GH replacement therapy.

There was no significance between groups in terms of total body BMD, t-score or z-score at baseline. The absolute levels of femur neck BMD and t-score were lower in the elderly patients. However there was no difference between groups

in femur neck z-score (BMD corrected for gender and age).This suggests that the lower femur neck BMD in the elderly patients was explained by the normal age –related decline in BMD.In the lumbar (L2-L4) spine, there was no between-group difference in BMD or t-score at baseline. However, lumbar (L2-L4) spine z-score was higher in the elderly compared with the younger GHD patients. This confirms that BMD, after correcting for the normal age –related decline ,is higher in elderly than in younger GHD patients[12,16,21].The responsiveness to the 3-year GH replacement at all skeletal sites ,measured, was similar in both study groups, total body BMD was unchanged after 3 –years, whereas lumbar (L2-L4) spine and femur neck BMD were increased. This demonstrates that GH replacement improves lumbar (L2-L4) spine and femur neck BMD in younger as well as elderly GH patients. Furthermore, the lack of significant effect of the 3-year GH replacement on total body BMD in both groups is in some accordance with the notion that GH affects bone mass and density predominantly at weight –bearing skeletal locations such as the lumbar spine and femur neck [14].Therefore, the possibility cannot be excluded that GH indirectly increased bone mass by improving physical activity level and muscle strength. We did not record whether the 3-year GH replacement increased activity level or muscle performance, but no attempt was made to influence the patients' physical activity levels during the study period. However, the magnitudes of the increases in lumbar (L2-L4) spine and femur neck BMD in response to the 3-year GH replacement were lower than those previously observed after bisphosphonate treatment of postmenopausal women [6].Therefore, studies with larger study populations than the present one are needed to explore whether GH therapy can reduce the risk of fractures in elderly GHD patients.GH replacement is motivated in elderly patients with impaired quality of life, body composition and serum lipid pattern .In several studies ,GH replacement has been shown to be similarly efficient in elderly and younger GHD adults in terms of increased bone mass and density. Since elderly GHD patients do not have reduced BMD compared with age-matched healthy subjects, this will not be an indication for GH therapy in most elderly GHD patients. However, BMD will increase in elderly GHD patients receiving GH replacement for other reasons. This gives further support for the notion that GH replacement is also useful in elderly GHD patients. The 3-year GH replacement increased lumbar (L2-L4) spine and femur neck BMD and BMC in elderly GHD adults. There are,however,distinct differences between elderly adults with GHD due to structural hypothalamic-pituitary disease and normal elderly subjects without severe GHD .Therefore, the extent to which long –term ,lower –dose GH treatment can improve bone mass in normal elderly subjects remains to be determined. In conclusion, this single- centre, prospective, open-label treatment trial demonstrates that 3-year GH replacement increases lumbar (L2-L4) spine and femur neck BMD and BMC in elderly GHD patients. These increases were of similar magnitudes as those in the younger control GHD adults and give further support for the notion that GH replacement is useful in elderly GHD patients. It remains, however to be investigated whether the increased BMC and BMD in response to GH replacement will reduce the risk of fractures in elderly GHD patients.

6. MATHEMATICAL RESULTS

Fig-1-A

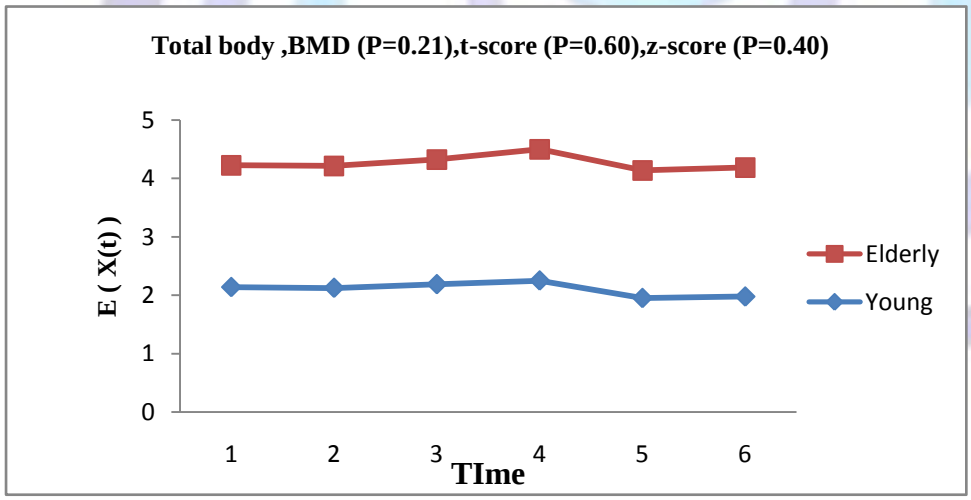

Fig-1-B

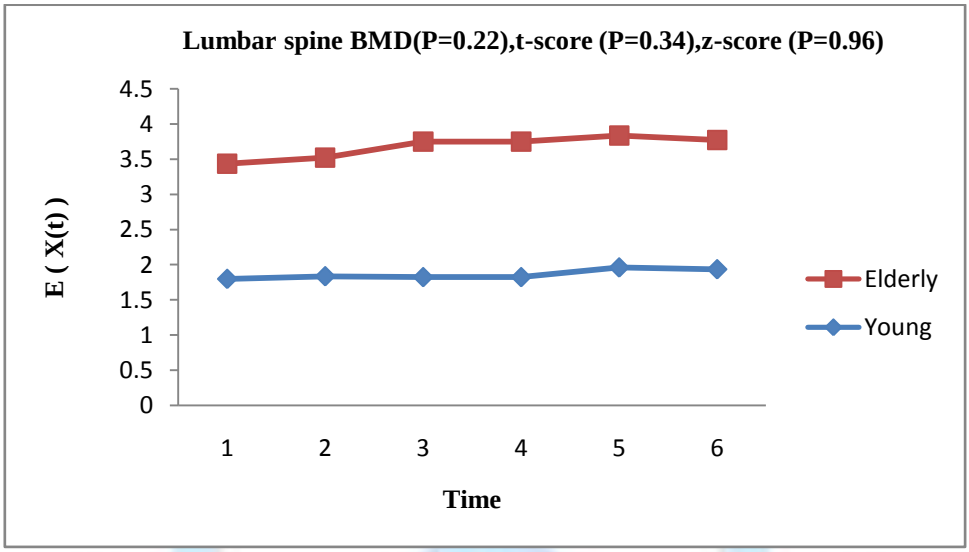

Fig-1-c

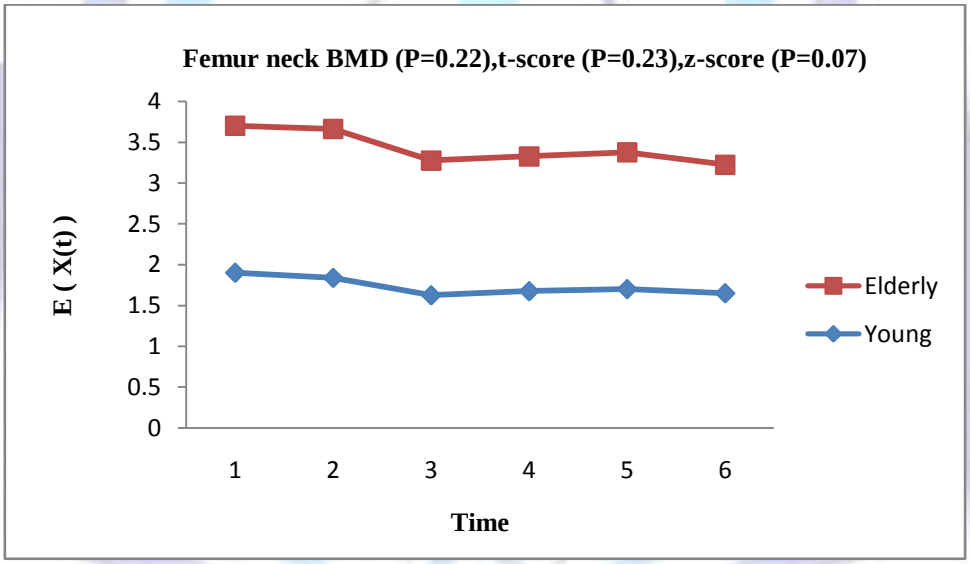

Fig-1-A

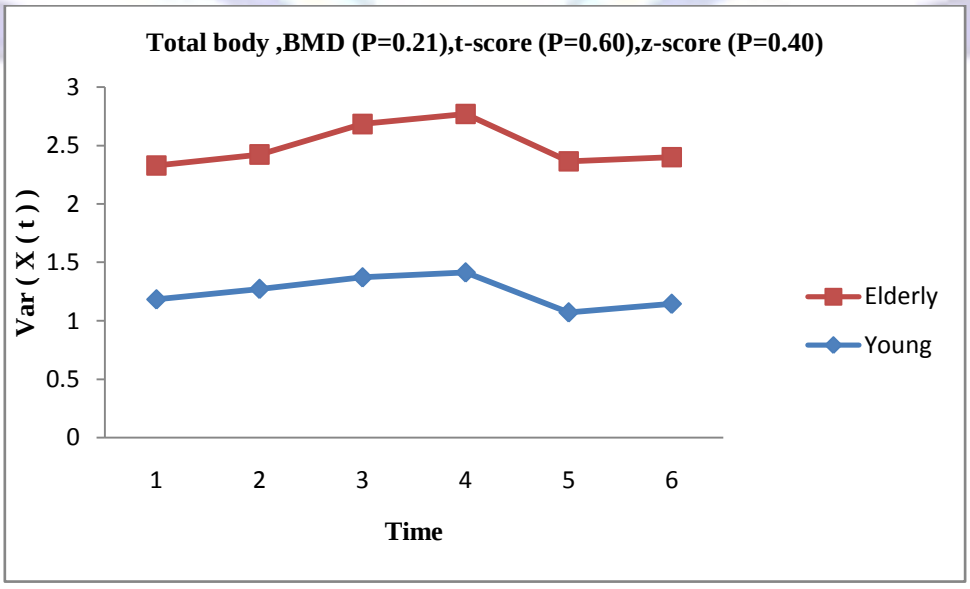

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Fig-1-B

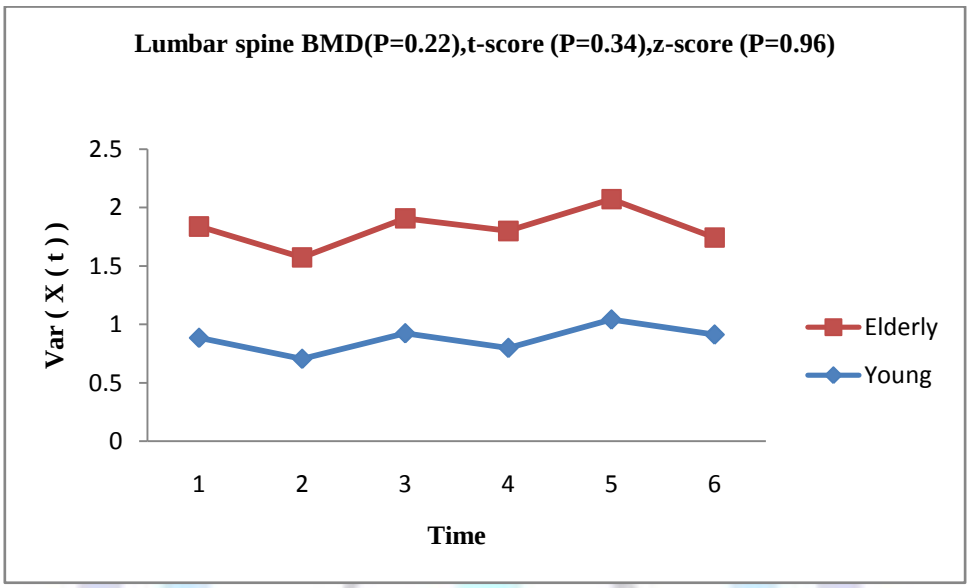


Fig-1-C

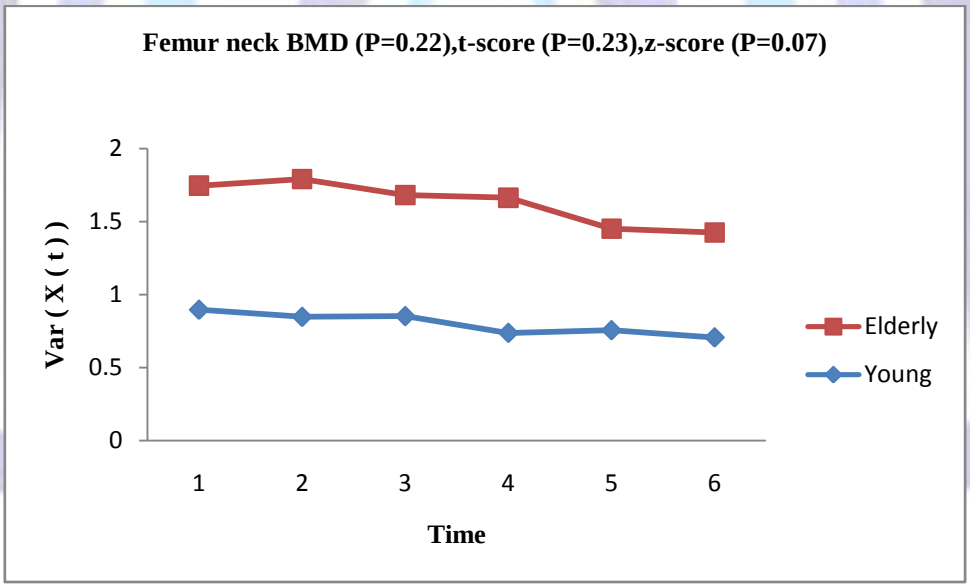
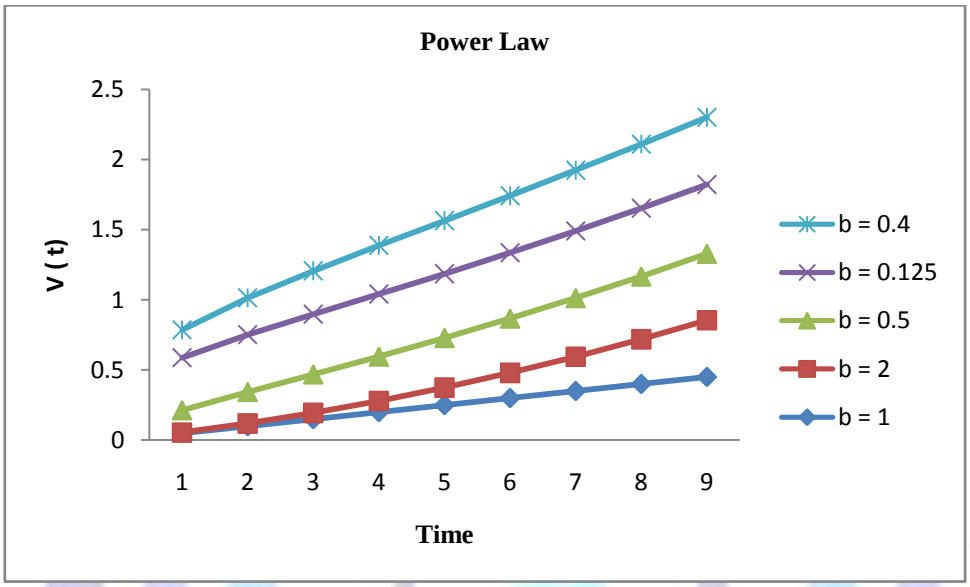


Figure - 2



7. CONCLUSION

The paper presents a stochastic gamma process model to account for both population (i.e sampling) and temporal variability associated with a degradation process that increases the probability of failure with aging of the structure. The proposed method is more versatile than the random variable damage rate model commonly used in the structural reliability literature. The reason being that the random rate model cannot capture temporal variability associated with the evolution of degradation. The paper also describes two methods for estimating parameters of the gamma processes to facilitate its practical application. The exposition of gamma processes presented in the paper would contribute to increase the usage of stochastic processes in the modelling of structural degradation. This study shows that GH replacement increases lumbar (L2 – L4) spine and femur neck BMD and BMC not only in younger but also in elderly GHD patients. Finally we conclude that our Mathematical result supports the notion that long – term GH replacement is also useful in elderly GHD patients.

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