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Diabetes and PCOS: Modeling the Effect of Hyperandrogenism on the Glucoregulatory System.

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I. ABSTRACT

Affecting 6-10% of all women of childbearing age, Polycystic Ovarian Syndrome (PCOS) is the leading cause of infertility in women. It is characterized by hyperandrogenism, chronic anovulation, and/or polycystic ovaries. Some physicians believe the syndrome manifests itself in three forms from mild to severe. Severe cases are easily diagnosed by the appearance of multiple ovarian cysts via sonogram. Milder cases can resemble adrenal disorders and even early menopause, complicating accurate diagnosis. Regardless of severity, recent medical reports show that over 80% of all PCOS women have insulin resistance (IR). IR increases the patients' risks for Type II Diabetes and cardiovascular problems, serious morbidity risk factors. While in-vitro fertilization and fertility hormones can address the reproductive challenges of PCOS, they do not prevent the syndrome from contributing to life-threatening conditions. A thorough mathematical model of the syndrome can reveal the mechanisms that contribute to the associated insulin resistance and increase the effectiveness of medical treatment.

Oral Glucose Tolerance Testing (OGTT) is the most commonly used diagnostic tool for insulin resistance in the medical community. Laboratory studies, using plasma insulin levels, suggest that glucose levels can remain steady despite fluctuations in insulin. Thus, glucose levels alone are insufficient for predicting low levels of IR. Pancreatic ability to increase insulin production on demand allows for the stabilization of blood glucose levels. In patients with IR, the increased demand on the pancreas for

extended periods exceeds the insulin production threshold of the pancreatic β-cells, maximizing their production levels. Only after β-cell function has maximized will the blood glucose levels increase. Plasma insulin levels can therefore indicate an increased demand on the pancreas before the increase in blood glucose levels appears, reflecting a patient's IR level earlier and more accurately than OGTT. Unfortunately, the plasma insulin test currently available is expensive and unreliable in non-laboratory settings. The significance insulin plays in PCOS is also supported by the success of diabetic pharmaceuticals on controlling the symptoms of PCOS once diagnosed.

Recent clinical studies of PCOS women imply a profound effect of Testosterone on the Glucoregulatory System. Testosterone in the primary androgen in women and is produced in the female ovaries by thecal cells of the follicles. In-vitro studies suggest that the thecal cells of polycystic ovaries produce four times the testosterone per unit of insulin as normal ovaries. Clinical evidence provides compelling evidence that this excess testosterone lowers skeletal muscle cell glucose uptake rate causing increased plasma glucose levels. This elevated glucose stimulates production of insulin so more glucose can be used by the skeletal muscles and stabilizes circulating plasma glucose levels. The resulting increase in circulating insulin stimulates a positive feedback loop of insulin-testosterone production that continues until β–ell insulin response to plasma glucose levels declines. While the onset of this cycle initially results in hyperinsulinemia (elevated insulin levels), it is not until β–cell response declines will glucose levels elevate to levels considered hyperglycemia (elevated plasma glucose) by current OGTT diagnosis criteria.

An existing mathematical model of the glucoregulatory system developed by Hernandez *et. al*, uses four differential equations to explain glucoregulatory functions. Here we expand this model to include a fifth ordinary differential equation that reflects ovarian production of androgens in response to insulin. The resulting system of equations identifies lower ranges of IR than OGTT alone. The benefit of such a model lies in its use of routinely tested androgen levels for early diagnosis of IR, eliminating the inconsistencies and additional cost associated with insulin level testing. Early diagnosis allows patients to reduce the glycemic load on the pancreas though lifestyle changes, a proven method of slowing if not completely stopping the progression to Type 2 Diabetes and cardiovascular disease in women with PCOS. This model, and its subsequent algorithm may allow medical practitioners to identify IR at stages when lifestyle and behavior adjustments can prevent the IR associated with PCOS from progressing to Type II Diabetes and Cardiovascular Disease, and consequently reduce the morbidity risk currently associated with PCOS.

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IV. INTRODUCTION

Type 2 Diabetes is a syndrome characterized by chronic hyperglycemia (elevated plasma glucose levels), impaired metabolism, and deficient insulin secretion and/or action (Bennett). The syndrome is associated with decreased pancreatic β-cell mass (responsible for insulin secretion) and the development of tissue resistance to insulin that develops into a state of elevated plasma glucose levels (Bennett). While either decreased insulin production or action may be the initial pathological processes that lead to Type 2 Diabetes, the causes of their development is not completely understood. Current clinical studies suggest that one of these causes may lie in hyperandrogenism.

Polycystic Ovarian Syndrome (PCOS) is an endocrine disorder effecting approximately 10% of reproductive age women and accounting for 90% of all hyperandrogenic (elevated Testosterone) states in women (Carmina). The most common symptoms include infertility, anovulation (absence of ovulation), irregular menstruation, hirsutism (excessive hair growth), and insulin resistance (IR) (Franks). While polycystic ovaries alone do not present critical health issues for most patients, clinical studies suggest a significant correlation between IR and elevated testosterone levels ($p < 0.0001$) (DeUgarte). It is this aspect of PCOS can lead to Type 2 Diabetes, obesity, hypertension and cardiovascular disease (Carmina). In vitro studies demonstrate an almost four fold increase in testosterone production by thecal cells in polycystic ovaries versus non-

polycystic ovaries (Medina). This relationship suggests a potentially significant variable in the understanding of etiology of Type 2 Diabetes.

TYPE 2 DIABETES MELLITUS AND INSULIN RESISTANCE

The mammalian glucoregulatory system maintains plasma glucose ranges by a delicate balance between glucose production from the liver and glucose uptake from plasma and in the intestines (Kahn). Plasma glucose uptake occurs in insulin-independent tissue, such as the brain, and in the insulin-dependent tissue found in muscle and fat. Of this insulin-dependent tissue, 75% of the glucose uptake occurs in skeletal muscle, while 5-15% occur in adipose tissue or fat accumulations throughout the body (Kahn). Insulin, secreted by the pancreas promotes glucose synthesis in the muscle and adipose tissue (Karam). Impairment of the muscle and adipose cells' response to insulin is believed to predispose a patient to clinical signs of hyperglycemia, in turn stimulating hyperinsulinemia (Karam). Insulin then activates the insulin-dependent tissue to increase its absorption rate of glucose with the intent of lowering plasma glucose levels (Kahn). In summary, a reduction in glucose uptake, as seen in patients with Insulin Resistance (IR), elevates plasma glucose levels in turn signaling pancreatic β-cells to produce insulin.

It is believed IR effects up to 20% of adults in the United States and significantly contributes to Heart Disease and Diabetes, the number one and number six leading causes of death in the United States, as well as being associated with many other diseases

(CDC). Recent findings in the study of IR have lead to the popular theory that it's significance transcends a pre-diabetic condition and includes a significant association with increased cardiovascular disease, dyslipidemia (abnormal blood lipid levels), atherosclerosis (arterial blood vessel disease), and many cancers (Hawkins). Prospective studies have shown that IR is always copresent in patients with Type 2 Diabetes and is the best predictor of the development as it predates the onset of Type 2 Diabetes by 10-20 years (Hawkins). Studies also show that the progression to Type 2 Diabetes can be delayed if not completely reversed with success rates increasing with earlier detection (Bennett).

DIAGNOSING INSULIN RESISTANCE

The most common diagnosis tool recommended by the World Health Organization (WHO) is the Oral Glucose Tolerance Test (OGTT), which gives only indirect evidence of IR (NDIC). The test comprises of a 12 fast followed by an orally ingested 100-g glucose load (WHO). A basal plasma sample is then taken, followed by 3 samples at 1 hour intervals (WHO). A 2-h > 200 mg/dL results quantifies a formal Diabetes diagnosis. Plasma glucose levels between 120 and 200 mg/dL suggest a form of IR, but are not classified under any specific diagnosis criteria, only considered an increased risk factor for Type 2 Diabetes (WHO).

Clinical studies often use fasting glucose and insulin levels with the Homeostasis Assessment Model (HOMA) (Wallace). HOMA is a mathematical model that returns an

insulin sensitivity value as a percentage of normal. HOMA has proven to be robust in assessing insulin resistance in patients over long periods of time with a coefficient of variation between 7.8% and 11.7% (Wallace). It is currently not used as a diagnosis in medical settings. It's requirement of three samples taken in five minute intervals to calculate a mean insulin level is a procedure many researchers substitute with a single basal measurement, disregarding the pulsating nature of insulin (Wallace). Current diagnosis levels vary widely with each study presenting additional ambiguity. DeUgarte *et al* define IR to be a HOMA score >3.90 (DeUgarte) as compared to Panidis *et. al*'s determination that IR constituted all values >2.00 (Panidis).

The most accurate diagnosis tool is the euglycemic insulin clamp technique. The euglycemic clamp is a surgical procure in which a person's glucose level is "clamped" at a predetermined level and insulin infusion rates are measured to determined the patients glucose uptake rate (Wallace). While the euglycemic clamp is considered the "gold standard" (Wallace). it's surgical nature makes it expensive, risky and impractical for clinical use (Goutham) despite it's effectiveness.

Consequently, "the lack of practical, inexpensive, reliable serum tests means that the diagnosis of insulin resistance can, at best, be made on the basis of strong clinical suspicion" (Goutham). For the possibly 60 million Americans, and countless others world-wide, currently effected by IR this leaves a void in medical diagnosis abilities making early detection difficult. It is currently suggested by the American Academy of Family Physicians that IR should be suspected in all patients with a family history of

diabetes, a personal history of gestational diabetes, impaired glucose metabolism (as indicated by OGTT), or Polycystic Ovarian Syndrome (Goutham).

POLYCYSTIC OVARIAN SYNDROME

Polycystic Ovarian Syndrome (PCOS) is the leading cause of infertility in the United States affecting up to 10% of the female population of reproductive age (Franks). Definitions and diagnosis criteria have evolved significantly over the last fifteen years. The most recent recommendation proposed at the European Society of Human Reproduction recommends first excluding some more uncommon, but well-characterized androgen excess disorders (For example: Cushing's Syndrome). The remaining patients are then diagnosed with PCOS when presenting at least two of the following three symptoms: hyperandrogenism, chronic anovulation, and polycystic ovaries (Carmina). This recommendation divides PCOS into three distinct phenotypes:

1. Classic PCOS: Hyperandrogenism and Chronic Anovulation
2. Ovulatory PCOS: Hyperandrogenism and Polycystic Ovaries
3. Idiopathic Hyperandrogenism: Hyperandrogenism with normal ovaries (Carmina)

These three disorders reflect 90% of all hyperandrogenic patients (Carmina). Overt symptoms, if present, may include menstrual disturbance, obesity, hirsutism, androgenic alopecia (abnormal hair loss), acne, and acanthosis nigricans (dark skin discolorations) (Franks). Endocrinological effects of PCOS include elevated Luteinizing Hormone (LH)

to Follicle Stimulating Hormone (FSH) ratio, Body Mass Index (BMI), serum androgens (most significantly total testosterone), serum insulin levels, and reduced insulin sensitivity (Carmina). The scale of severity for each begins with the milder phenotype (Idiopathic Hyperandrogenism) and increases to the most severe phenotype (Classic PCOS) (Carmina).

THE IR – PCOS CYCLE

It is currently believed that PCOS begins with a genetically determined excess secretion of ovarian androgens in childhood, puberty, or possibly in utero (Franks). Evidence suggests the increased androgen influences early follicle maturation, in turn compromising thecal cell function (Franks). Thecal cells, found on the exterior of the ovarian follicle, produce testosterone (Medina), the primary female androgen, in response to activation of insulin receptors (Medina), (Figure 1.1) So begins a "self-propagating cycle of abnormal follicular growth and function" (Franks).

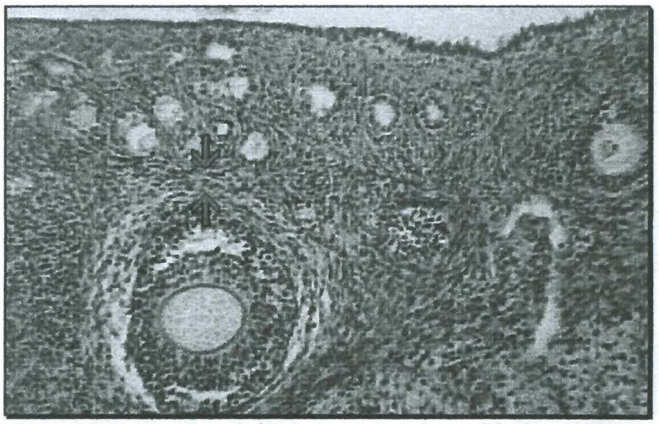


Figure 1.1: Ovarian Follicle cross section with thecal layer identified.

Beyond this insulin receptor / thecal cell interaction studies suggest that up to 80% of all patients with PCOS are insulin resistant (Carmina), making them potentially at a seven times higher risk of developing Type 2 Diabetes (Franks). This is further supported by success of insulin sensitizing treatments, such as Metformin, in lowering circulating androgen levels and normalizing menstruation in PCOS women (Median). It is this glucoregulatory / reproductive connection suggested in PCOS patients on which we focus our modeling study.

Clinical data of PCOS patients conducted by DeUgarte *et al*, and Panidis *et. al* strongly suggest a significant correlation between clinical levels of testosterone and insulin. In the study conducted by DeUgarte *et al* from 1996 to 2002, 217 clinically diagnosed PCOS patients' biochemical features were compared against 260 control patients to determine the relative prevalence of IR in PCOS patients (DeUgarte). Mean insulin levels of 22.7 μU/mL ± 19.5 sd were found in PCOS women versus a mean of 10.4 μU/mL ± 7.5 in control subjects, with a p-value for significance of <0.0001 (DeUgarte). They also found that PCOS patients were more likely to have higher androgen levels. Control ranges for total testosterone levels are defined as between 0.69 to 2.7 nmol/L and free testosterone (Free T) defined as .03 - .04 nmol/L. (Source?) DeUgarte defines hyperandrogenism by a Total T level > 2.96 nmol/L and Free T level > 0.026 nmol/L (DeUgarte). The significance for both Total T and Free T, in PCOS patients, have p-values < 0.0001 (DeUgarte) Similar results were found by Panidis *et. al* in their study of 93 PCOS versus 36 control subjects. For this group PCOS women had

Total T levels of 3.1788 nmol/L ± 0.7596 versus 1.6611 nmol/L ± .2585 for the control group (Panidis). In this study HOMA and area under the curve (AUC) for insulin is reported, in contrast to insulin levels. While HOMA are less significant, possibly due to lower glucose in presence of hyperinsulinemia, the AUC for insulin has a significance of <0.02 for PCOS versus control (Panidis).

In addition to a positive correlation between Total T and Insulin levels, studies suggest a synergistic relationship. Preliminary evidence began to arise after Metformin, a insulin sensitizing pharmaceutical, was approved for use in the U.S. by the FDA in December 1994 (FDA). It was found that patients with PCOS reduced their plasma insulin levels from an average of 17 ± 3 μU/mL to 9 ± 2 μU/mL after 42 days of Metformin treatment (p-value=0.03) (Medina). The same study showed Total T decreasing from 3.123± .59 nmol/L to 2.3596 ± .49 nmol/L post Metformin treatment (Medina). The results of this study suggest that increased Total T is a result of insulin stimulation (Medina).

V. METHODS

MODELING THE GLUCOREGULATORY SYSTEM (Hernandez *et al*)

Attempting to model the relationship between insulin and testosterone necessitates a thorough understanding of the glucose regulatory system. In 2001, Hernandez *et al* presented an extended model of Topp, *et al* that successfully contributes to the study of IR and Type II Diabetes by qualitatively and quantitatively describing different pathways to Type II Diabetes. While formally awaiting publication, the paper in it's entirety can by found at: http://www.csupomona.edu/~swirkus/Diabetes.pdf. The system is in the form of the following four equations:

1) $$\frac{dG}{dt} = a - (b + cRI)G$$

2) $$\frac{dI}{dt} = \frac{d\beta G^2}{(1+R)(e+G^2)} - fI - fRI$$

3) $$\frac{d\beta}{dt} = (-g + hG - iG^2)\beta$$

4) $$\frac{dR}{dt} = j(1-R) - kIR - lR$$

Model 2.1: Hernandez et al presentation of the modified Topp et al model of the glucoregulatory system.

where G represents fasting plasma glucose levels (mg/dl), I represents fasting plasma insulin levels (μU/ml), β in the pancreatic β-cell mass (in mg), and R in the fraction of

insulin receptors on the surface of muscle cells (Hernandez). Normal physiological parameters for an average healthy person are:

Table 2.1: Default Parameter Values for Model 1

Parameter	Value	Biological Interpretation
a	864	glucose production rate by liver when G=0
b	1.44	glucose clearance rate independent of insulin
c	0.85	insulin induced glucose uptake rate
d	43.2	β-cell maximum insulin secretion rate
e	20,000	inflection point of sigmoidal function
f	216	whole body insulin clearance rate
g	0.03	β-cell natural death rate
h	5.727502102E-04	determines β-cell glucose tolerance range
i	2.552312868E-06	determines β-cell glucose tolerance range
j	2.64	insulin receptor recycling rate
k	0.02	insulin dependent receptor endocytosis rate
l	0.24	insulin independent receptor endocytosis rate

(Hernandez)

The model successfully predicts levels of glucose, insulin, β-cell mass, and insulin receptors under normal conditions reflecting physiological equilibrium states (See Figure 3.1). Under IR conditions where insulin induced glucose uptake rate (parameter c) is significantly reduced, the model also predicts the onset of diabetes (See Figure 3.2). In addition to the successful prediction of diabetic states, benefits of this model include the original consideration of insulin receptors, accuracy in predicting physiological β-cell mass, and the ability to explore its behavior under various physiological conditions "*in silico*".

INSULIN'S FEEDBACK EFFECT ON TESTOSTERONE PRODUCTION

Our challenge lies in modeling the influence of Total T on this system. In vitro studies conducted by Medina *et al* provide a critical piece of data. In their study thecal cells were harvested and cultured from the follicles of PCOS and control ovaries (Medina). In a serum-free culture medium, 10^6 cells/mL of ovarian thecal cells were stimulated with 20 μU/mL of insulin (Medina). Time trials reveal a delayed reaction to stimulation, where thecal cells did not respond to insulin stimulation until 6-9 hours of incubation, reached peak testosterone synthesis at 12-16 hours, and slowly declined after 48 hours (Medina). This delay suggests thecal cell testosterone production is desensitized to the rapid fluctuations we see in plasma insulin levels. Both cultures reflect basal testosterone production before insulin (exact values reported for PCOS cells of 1.2 pg/mL, control not reported). However, that PCOS thecal cells compared with control thecal cells produced approximately 4 times the testosterone under stimulation (13.2 ± 1.4 pg versus 3.7 ± 1.5 pg for control thecal cells) with a significance of $P < 0.005$ (Medina). The time dependent and dose response curves for both sub-groups were similar in shape with the significant difference found in the maximum production of testosterone (Medina). We model these results with the following simple equation for Testosterone:

5) $$\frac{dT}{dt} = m(T_\alpha - T)$$

where T represents testosterone in nmol/l and the parameter m takes the value of 1 or 4 (Medina), to distinguish between control and PCOS patients. The insulin dependent equilibrium value T_α is given by the sigmoidal function: and the parameters are given in Table 3.2.

6)
$$T_\alpha(I)=n+\frac{o(e^{(I-p)})}{1+e^{(I-p)}}$$

Table 2.2: Parameter Values for Equation 5

Parameter	Value	Biological Background
n	.005	Determines minimum testosterone production (Medina)
o	3.14	Testosterone unit conversion factor
p	10	Insulin stimulus for half Maximum testosterone Production

TESTOSTERONE FEEDBACK ON THE GLUCOREGULATORY SYSTEM

To complete our model of the insulin testosterone feedback loop we use clinical data from a study 13 female gender reassignment candidates who were administered injections of 250 mg of testosterone esters to induce hyperandrogenism (Heine). At one week and at four months post treatment, euglycemic clamps were performed to assess IR and glucose utilization rates (Heine). Glucose utilization rates decreased from 3.5 ± 1.2 mmol/kg LBM·h before treatment to 2.6 ± 0.9 mmol/kg ($P < 0.0001$) after four months of hormone treatment (Heine). This result suggests that the parameter *c* representing insulin induced glucose uptake rate, is reduced by androgen levels. We therefore introduce a T term into the equation for glucose uptake rate which decreases insulin

dependant glucose uptake rate as testosterone increases (Equation 7). This leads to our full model reflecting female androgenic effects on the glucoregulatory system.

7) $$\frac{dG}{dt} = a - (b + (\frac{c}{T+1}) RI) G$$

2) $$\frac{dI}{dt} = \frac{d\beta G^2}{(1+R)(e+G^2)} - fI - fRI$$

3) $$\frac{d\beta}{dt} = (-g + hG - iG^2)\beta$$

4) $$\frac{dR}{dt} = j(1-R) - kIR - lR$$

8) $$\frac{dT}{dt} = m\left[n + \frac{o(e^{(I-p)})}{1+e^{(I-p)}}\right] - T$$

Model 2.2: Expanded model reflecting female androgenic effect on the glucoregulatory system The system is simulated using the Runge-Kutta method of approximation, with the ode45 algorithm on MatLab Student version 7.0.1.

VI. Results

MODEL OF HERNANDEZ *et al*

This original system is reported to have three equilibrium points with two stable nodes and a saddle point (Hernandez). The first stability point occurs at pathological initial conditions. The second occurs within physiological norms (Hernandez) and therefore, it is the behavior of the system under the associated initial conditions that present the most accurate predictions. With initial conditions set to that of a non-diabetic person ($\beta = 850$, I=15, G=85, R=.9), the plot of the trajectories over a 3 day period, shows each variable traveling directly towards it's equilibrium state (see Figure 3.1) (Hernandez).

We are also interested in the model's ability to reflect diabetic states. While Hernandez reports two pathways to diabetes, we will focus our attention to behavior under changes to parameter c, the insulin sensitivity parameter. In their study they demonstrate that adjusting the insulin sensitivity parameter *c* to below normal values (0.1) induces glucose levels to elevate to diabetic ranges, while decreasing β-cell mass and insulin levels (Figure 3.3). We note here that eventual equilibrium values for this simulation are pathological, due to the unboundedness of the β-cell equation of the original Topp *et al* model, yet the behavior of the system is consistent with current studies on the mid-range time scale (Hernandez).

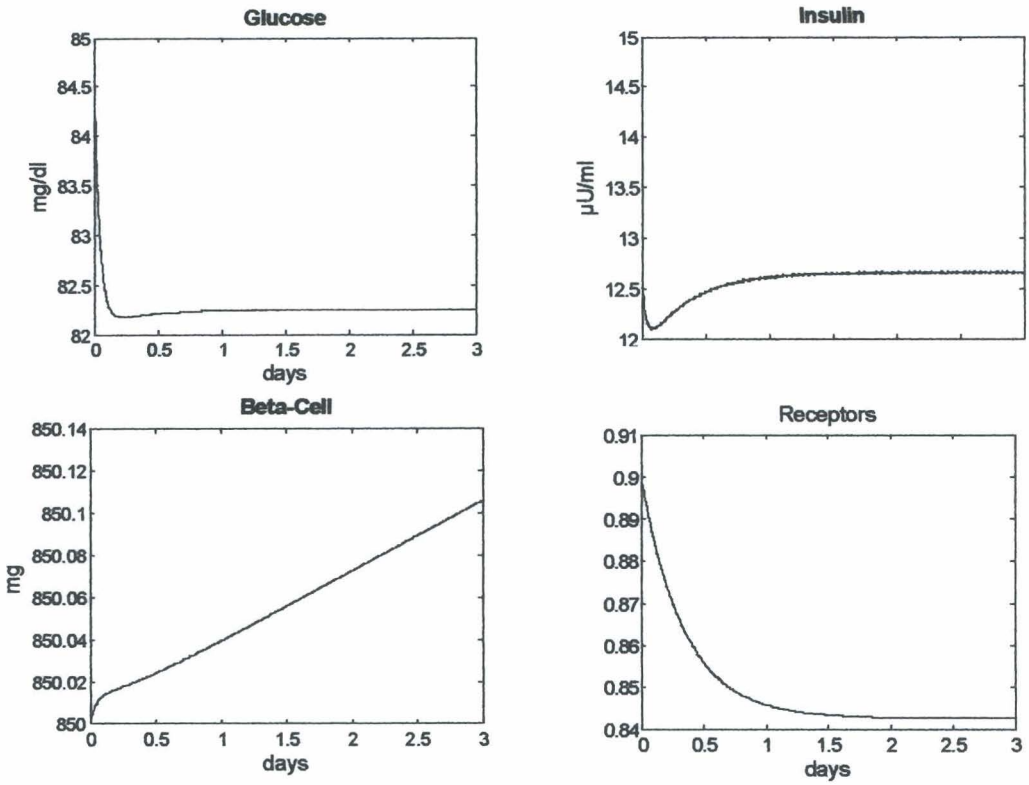


Figure 3.1: Simulation of Model 2.1 under normal parameters as defined in Table 2.1 and normal initial conditions. Run for 3 days to show the physiological equilibrium the system achieves.

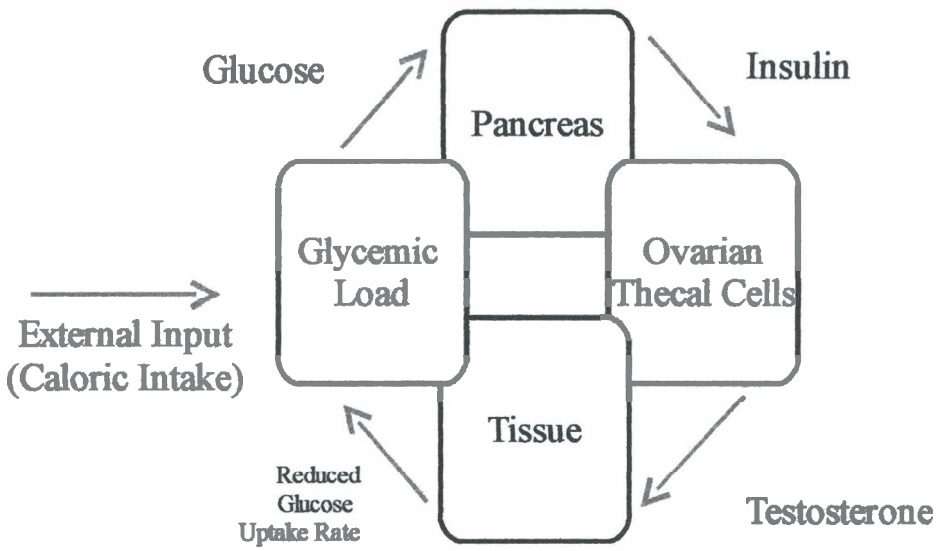


Figure 3.2: Hyperandrogenism's circular pathway to Diabetes

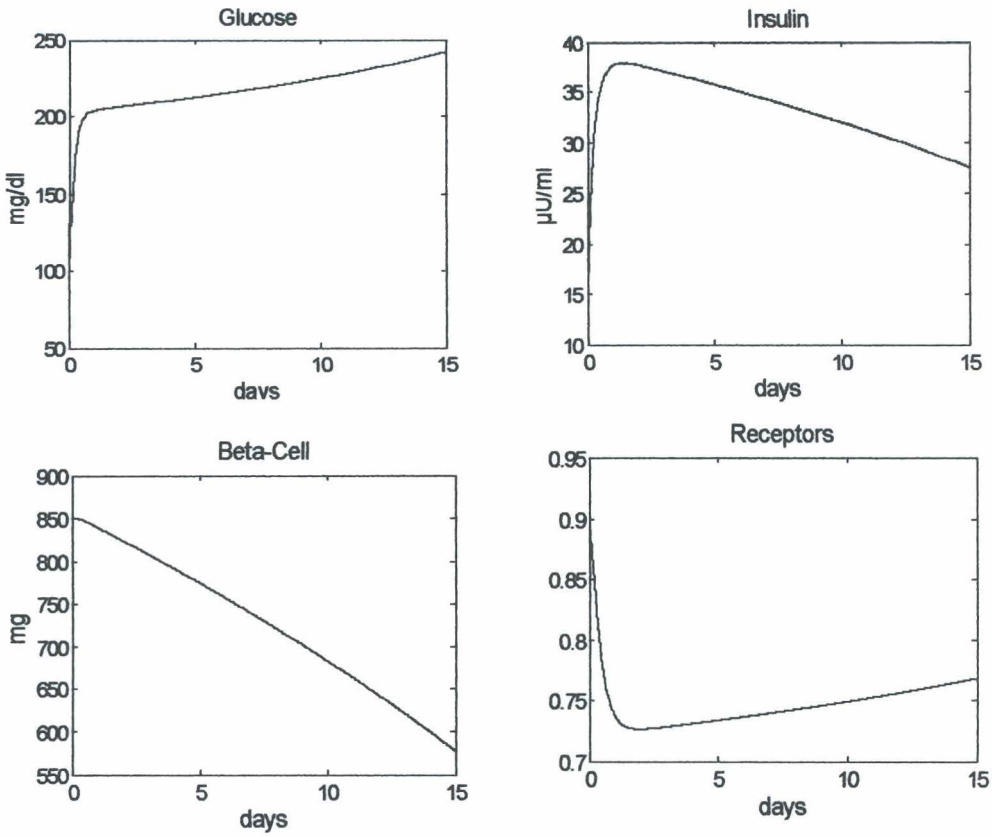


Figure 3.3: Simulation of Model 2.1 with parameter c decreased to 0.1 reflecting the decline in glucose uptake rate progression to Type 2 Diabetes with normal initial conditions. Run for 15 days.

EXPANDED MODEL

Considering testosterone's effect on the glucoregulatory system is a relatively new development. Many studies of PCOS find a strong correlation between testosterone and insulin levels. Examining "*in-vitro*" thecal cell cultures (Medina) and androgen treatment trials (Heine) support a self-propagating testosterone / insulin relationship in which direct and indirect causation can be supported for modeling. Identifying this relationship

expands our current knowledge of the pathogenics of the glucoregulatory system and it's relationship with the endocrine functions of the reproductive system.

This additional information reveals a previously unconsidered pathway to Type 2 Diabetes, namely a circular relationship that steadily increases until β–cell insulin production can no longer prevent chronic hyperglycemia (see Figure 3.2). Our mathematical model (Model 2.2) is based on this circular relationship. In severe hyperandrogenous states, as found in many PCOS patients, the excess testosterone production desensitizes muscle tissue to the effects of insulin, elevating plasma glucose levels, stimulating more insulin production, that in turn stimulates ovarian production of testosterone. It is helpful to note that this pathway can occur regardless of external input to the glucoregulatory system.

MODEL BEHAVIOR

In the following simulations we first demonstrate the behavior of Model 2.2 under normal initial conditions, parameters as defined in Tables 2.1 and 2.2, with parameter m=1 to reflect a non-PCOS patient. The expansion of the model to included testosterone's impact behaves very similarly to the model by Hernandez *et al* (Figure 4). It is worthy to note the equilibrium points each variable is approaching. Glucose is well within normal parameters at a level of 86 mg/dL. Insulin levels off at approximately 14 μU/mL, with the fraction of Receptors on the cell surface reaching 0.84. β-cell mass continues to increase without bound, a problem in the original model that continues to

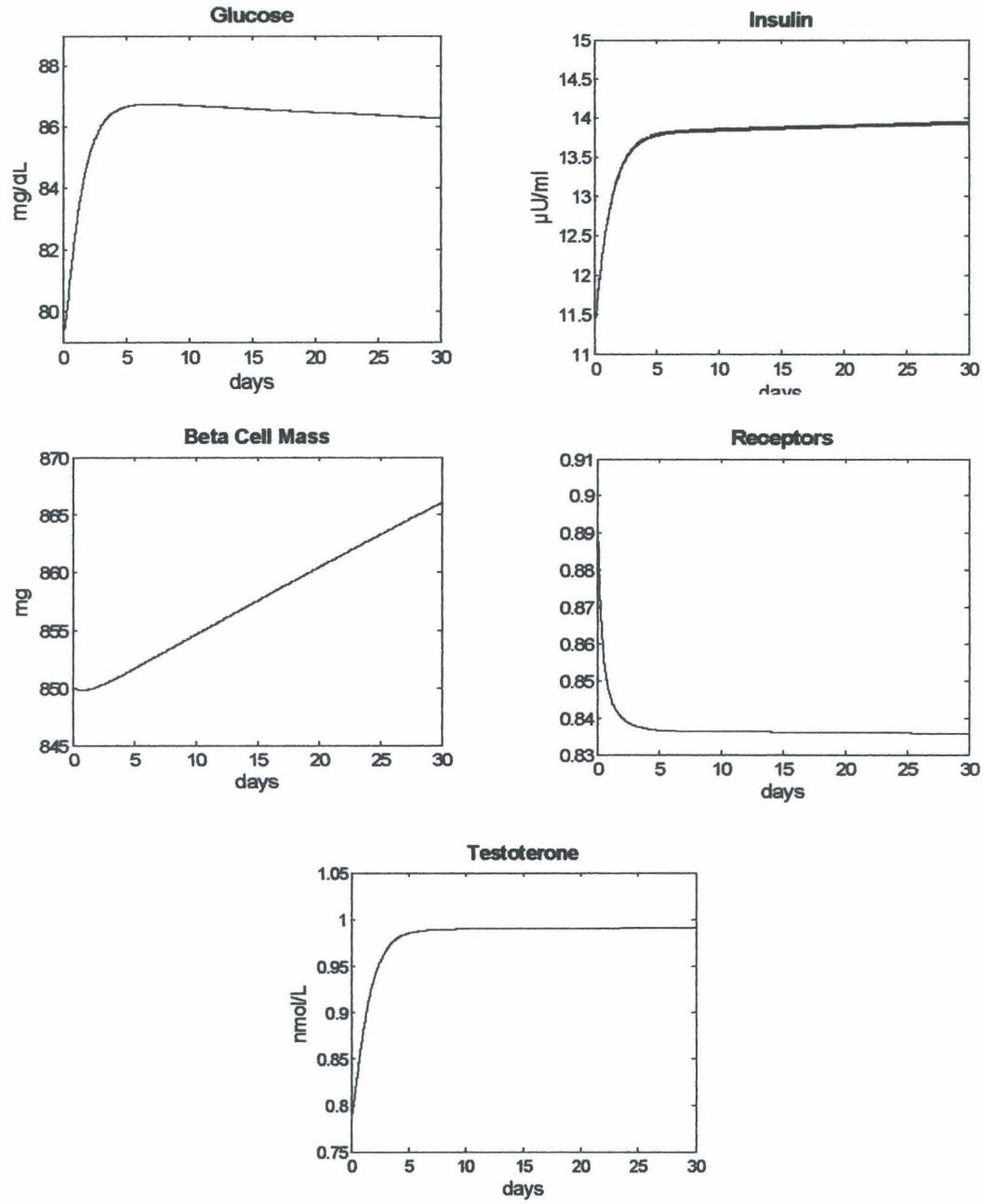


Figure 3.4: Expanded model behavior under normal parameters and initials conditions.

occur but does not effect the significance of the simulated behavior on the mid-range time scale.

Further benefits of the expanded Model 2.2 lie in it's ability to reflect the progression of abnormal glucose metabolism as seen in patients with PCOS. By changing parameter *m* from 1, reflecting a non-PCOS patient, to 4, reflecting a PCOS patient, it is evident that this increased testosterone production rate reflects the circular relationship between the endocrine functions of the reproductive system and the glucoregulatory systems (Figure 5). In Figure 5 you will note Type 2 Diabetes and IR glucose diagnosis levels are referenced. The estimated solution to Model 2.2, as solved on MatLab Student Edition 7.01. using the ode45 algorithm, very closely resemble the Model 2.1 simulation of IR progression into Type 2 Diabetes while reflecting the clinical data observed from PCOS patients. We see in this simulation that under PCOS conditions, with a four-fold increase in testosterone production by ovarian thecal cells, that the patient's glucose reaches IR levels within 5 days, progressing slowly towards full onset Type 2 Diabetic levels towards the end of the thirty day simulation. It is also observable that once β-cell mass begins to decline, Insulin production follows suit. Receptors dynamics also respond by increasing the fraction of receptors on the cell surface. The equilibriums achieved by each variable are quite similar to those of the Model 2.1 simulation of a decreased glucose uptake rate, as graphically represented in Figure 3.3. Testosterone's delayed reaction to insulin fluctuations extends the progression by decreasing the slope of the variables' trajectories. This gradual progression is more stable in simulation and

physiologically realistic. Through this simulation we can also examine the slow progression of PCOS related IR as seen in clinical trials.

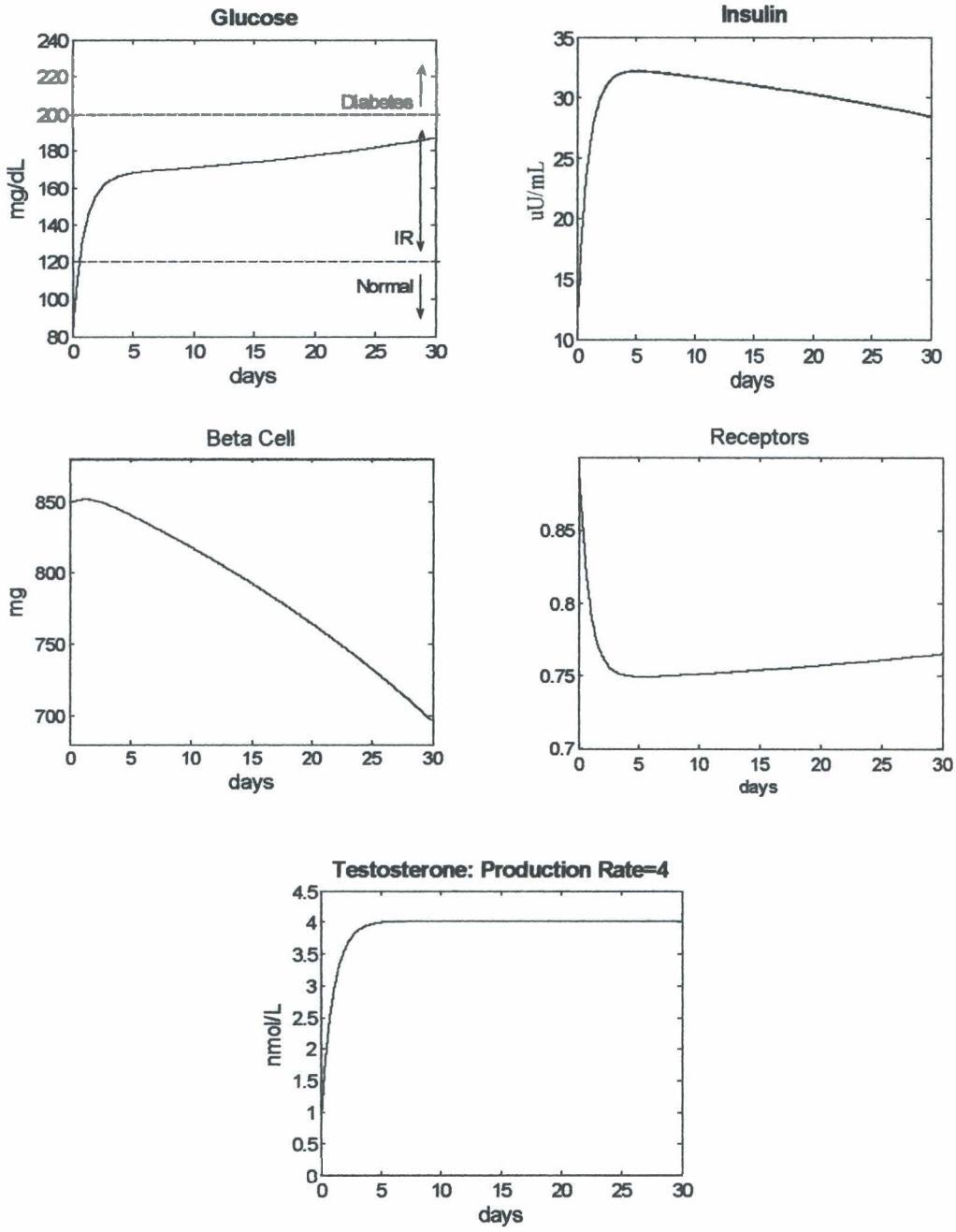


Figure 3.5: Model 2.2 simulation of Testosterone's effect on the Glucoregulatory system as seen in patients with PCOS.

able to show the importance of testosterone in understanding the dynamics of the glucoregulatory system and the progression of Type 2 Diabetes. In doing so, we have also revealed a potentially important early diagnosis tool in identifying IR. Based on our model, testosterone's delayed reaction to insulin levels, provides a measure of mean plasma insulin levels, therefore avoiding the need for multiple samples that HOMA requires. Paired with OGTT, testosterone's ability to track it's own insulin dependent equilibrium, can provide medical practitioners with an additional tool for IR diagnosis. Implementation of this screening parameter can help reduce the need for suspicion in diagnosing IR, increasing the success of early detection and treatment in the fight against Type 2 Diabetes.

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