1. Almost 60% (600/1000 persons) of the human population is thought to have a genetically-influenced disease representing a major impact on the economy and health services all over the world. Identification of genes implicated in genetic and genetically influenced diseases facilitates early prediction of risk, diagnosis and provides hope for the development of drug- or gene-based therapies. Complex diseases are usually caused by multiple disease-susceptibility gene, environment factors and interaction between them.

2. Obesity can be seen as the first wave of a defined cluster of non communicable diseases called "New World Syndrome," creating an enormous socioeconomic and public health burden in poorer countries. The World Health Organization has described obesity as one of today's most neglected public health problems, affecting every region of the globe.

3. Obesity has reached epidemic proportions globally, with more than 1 billion adults overweight - at least 475 million of them clinically obese - When Asian-specific cut-off points for the definition of obesity (body mass index >28 kg/m^2) are taken into account, the number of adults considered obese globally is over 600 million- and is a major contributor to the global burden of chronic disease and disability.

4. Obesity has reached epidemic proportions in India in the 21st century, with morbid obesity affecting 5% of the country's population. Urbanization and modernization has been associated with obesity. In Northern India obesity was most prevalent in urban populations (male = 5.5%, female = 12.6%), followed by the urban slums (male = 1.9%, female = 7.2%). Obesity rates were lowest in rural populations (male = 1.6%, female = 3.8%)
5. The effects of obesity not only relate to chronic medical conditions but also have been strongly related to reproductive problems. Potential effects of increased body mass index (BMI) in men on fertility have not been subjected to the same degree of research as female obesity. There is growing evidence over the years that suggest a trend towards deterioration in semen quality in relation to obesity. Several hypotheses have been proposed, and male obesity was suggested as a strong factor. Several studies have linked male obesity to poor semen quality and male infertility. The mechanisms that explain the relation between obesity and male infertility are not fully understood. Higher DNA fragmentation indexes in obese males, increased oxidative stress, and hormonal imbalance have been suggested as possible mechanisms of obesity-associated subfertility.

6. In India about 15–20% of married couples known to be sub/infertile category, selected for medically assisted reproductive technology (MART). However, a substantial portion of infertile patients still remain without help for various reasons such as lack of adequate treatment options and their accessibility, high cost and fear of conceiving and bearing potentially abnormal offspring. This is despite the fact that over the years MART has become useful for couples with infertility, with a good success rate of about 20 to 30% globally. There is a need for a multidisciplinary comprehensive infertility care, which should also involve structured management strategies, and this should include clinical evaluation, genetic diagnosis (PGD), genetic counselling, patient education, informed consent and most appropriate and cost effective MART approaches to infertility treatment.
7. In the light of this, the author has made an attempt of systematic genetic and molecular analysis of male obesity associated with infertility in Mysore, South India.

8. The present investigation was undertaken in obese men with/without infertility in Mysore, with objectives of analysis of pedigree, assessment of seminal Reactive Oxygen Species (ROS), analysis of inflammatory pathway by measuring the seminal interleukin 6 (IL-6) level, analysis of seminal Protamine-1 (P1) and Analysis of the three exons of the candidate gene in order to find single nucleotide polymorphism (SNP) associated with any of the condition in the present investigation.

9. The literature survey about the known pathophysiology and genetic factors involved in obesity and male infertility and possible physiological and genetic impacts of obesity on fertility pathways in men has been reviewed.

10. A total 250 confirmed subjects with obesity and/or infertility including obese infertile males, non-obese infertile, obese fertile males and controls were considered for the present study from Medivawe IVF and fertility research hospital, Harsha infertility clinic, obesity clinic and Gyms in Mysore. The ages of the patients ranged from 20 to 45 years. Aged match controls consisting 100 males with normal BMI and proved fertility were also randomly selected from different locations of Mysore city, irrespective of their ethnic background. The consent letter was obtained from the participants before including them in the study. This study was approved by the Institutional Human Ethical Committee of University of Mysore.

11. The diagnosis of infertile patients based on their semen characteristics were classified as aspartame, azoospermia, oligozoospermia, asthenozoospermia,
teratozoospermia, oligoasthenozoospermia and oligoasthenoteratozoospermia according to WHO guidelines. The obesity condition also were classified based on BMI as overweight, obese type I, obese type II and morbid obese.

12. Analysis of clinical manifestation of all conditions revealed the following information:

- Azoospermia was most prevalent condition among obese infertile as well as non-obese infertile groups.
- A logistic regression test revealed that among lifestyle factors considered for this study, smoking had a significant negative effect on semen parameters in both infertile groups when compared to other factors like alcohol consumption, laptop and mobile usage.
- Obese infertile patients had lower semen quality compared to other groups. Further, obese fertile cases showed slight decrease semen parameters compared to non-obese fertile males.

13. Pedigree analysis of obesity/infertility in 250 subjects’ families and 100 non-obese fertile males as controls revealed the following:

- The pedigree of the infertile subjects was analyzed without considering obesity in obese infertile group and results revealed that family history of parental consanguinity, proband consanguinity and both parental and proband consanguinity were significantly associated with male infertility. None of the paternal and maternal and sibling family history of infertility were significantly associated with proband’s infertility when compared to control group.
- About 22% of the families had consanguineous marriage in their parents, which was associated significantly with higher risk of infertility incidence as compared to non-consanguineous families.
• About 26% and 8% of the families had proband consanguinity and both parental and proband consanguinity in their families respectively, which similarly was associated with higher risk of infertility as compared to non-consanguinous families.

• In another analysis, pedigree of patients was analyzed to find the pattern of inheritance of male obesity among obese fertile males. It was observed that all individuals and their maternal, paternal, sibling family history as well as parental consanguineous marriages were significantly associated with proband’s obesity as compared to control group.

• To analyze the pattern of inheritance for obese individuals associated with infertility, their pedigree was analyzed. It was observed that only sibling family history, parental and proband consanguineous marriage was associated with higher risk of this combined condition when compared to control group.

14. The semen samples of 140 subjects from obese fertile, obese infertile and non-obese infertile groups and 100 controls were studied for ROS and LPO measurement which revealed the following:

• ANOVA tests revealed that the seminal levels of ROS and LPO were higher compared to other study groups and the difference was statistically significant.

• Independent t-tests revealed that obese fertile group also showed elevated levels of LPO and ROS in their semen samples when compared to non-obese fertile males.

• The Pearson correlation test showed a positive relationship between BMI and seminal level of LPO and ROS.

15. Analysis of seminal IL-6 level with 140 and 100 controls revealed the following:
• An ANOVA followed by Post Hoc tests revealed a significant elevation of IL-6 levels in semen of obese infertile males compared to other study groups.

• An independent t-test revealed a higher level of IL-6 in obese infertile males compared to non-obese fertile males as well as a raise in the seminal level of IL-6 in the obese fertile group compared to non-obese infertile group.

• The Pearson correlation test showed a significant positive relationship between seminal level of IL-6 and BMI.

• To find the association between other lifestyle predictors, regression analysis revealed that all lifestyle predictors together had a significant effect on IL-6 as a response variable. Regression coefficient showed that BMI was the best predictor for variance in IL-6 level.

16. Analysis of sperm PRM1 levels in 120 cases and 50 controls revealed the following:

• It was noted a significant difference for PRM1 within study groups and obese infertile group showed a lower mean value for PRM1. A pair wise comparison analysis showed lower levels of PRM1 in the obese fertile group compared to non-obese fertile. The difference was significant at the 95th percentile level.

• Although, Pearson correlation analysis showed a negative correlation between BMI and PRM1 level but it is very difficult to consider the obesity as a main predictor for such variation while infertility itself can be an important reason.

17. Analysis of the three exons of the \textit{JHDM2A} gene in order to find single nucleotide polymorphism (SNP) or variation in 200 samples and 50 controls revealed:

• No variation was observed in exon 23 and 24 of \textit{JHDM2A} with conditions under study when compared to the normal sequence in database.
• In the present study, 11 cases from all conditions including obese infertile, non-obese infertile, obese fertile and control subjects were observed to be associated with a variation in exon 25 of JHDM2A gene.

• Since there is a lack of studies on JHDM2A gene in human model, exom sequencing of this gene in male patients with metabolic disorders and infertility will be very much helpful to find a particular subset of SNPs associated with mentioned conditions in Indian population.

• Variations in exon 25 among control males who had central obesity despite of having BMI within normal range demonstrate that these variations in JHDM2A gene may partly contribute to some kind of monogenic male obesity but further analysis including exome sequencing or using next-generation sequencing techniques is suggested for thorough analysis of this gene in human obese and non obese as well as infertile males compared to other genes.