Unit IV – Problem 2 – Genetics: Genetic Predisposition to Type-II Diabetes

- **What is diabetes mellitus?**
  - It is a multi-factorial disorder related to carbohydrate metabolism, characterized by hyperglycemia and resulting from:
    - ✓ Altered production of insulin (type-I, LADA or advanced stage of type-II diabetes).
    - ✓ Insulin resistance (type-II).
- **What are the major forms of diabetes?**
  - **Type-I (insulin-dependent).**
  - **Type-II (insulin-independent).**
  - **Gestational diabetes (transient with pregnancy).**
- **Pathogenesis of diabetes**: there must be a genetic predisposition and an environmental trigger (such as a viral infection). Notice that there is a 75% chance for an identical twin to develop type-II diabetes when a twin sibling has type-II diabetes.
- **Type-II diabetes:**
  - Composing 90% of all diabetic cases.
  - Associated with obesity and certain racial and ethnic backgrounds (more among pima Indians, African-americans and asian-americans). It is also very common among GCC countries.
- **Family history in type-II diabetes:**
  - Type-II diabetes has a more significant genetic basis than type-I, but it depends more on environmental than genetic factors.
  - Lifestyle (e.g. sedentary, diet rich in fat, processed carbohydrates and low in fibers) is the biggest environmental trigger for type-II diabetes.
- **Pathogenesis of type-II diabetes:**
  - The inheritance of type-II diabetes is polygenic (not a single genetic disorder).
  - There is both insulin resistance and impaired insulin secretion.
  - The disease is strongly associated with obesity (increased adipose cells will increase the release of pro-inflammatory mediators such as IL-6 and leptin. Also, the secretion of the anti-inflammatory adiponectin will be reduced).
- **Genetic factors in type-II diabetes:**
  - **Classification of genes:**
    - ✓ Diabetogenic genes: they are essential and relatively specific but may not be sufficient by themselves to cause diabetes. Included are alteration in the activity of glucokinase.
    - ✓ Diabetes-related genes: they are not specific (not limited to patient with diabetes). Included as genes regulating appetite, energy expenditure and intra-abdominal fat accumulation.
  - **The most important two genes linked to type-II diabetes are:**
    - ✓ TCF7L2: a transcription factor and member of the Wnt signaling pathway.
    - ✓ PPARG: Peroxisome Proliferator Activated Receptor Gamma.