1.0 INTRODUCTION

Type-2 diabetes (T2D) is becoming one of the fastest-growing major non-communicable diseases (NCDs) adversely affecting human life and well-being globally, in a multitude of ways. The latest epidemiological data shows its worldwide prevalence as 463 million and is projected to reach 700 million by 2045 (Saeedi et al., 2020). The global burden of diabetes, considering the treatment costs and loss of productive years for 2015 was estimated to be US$1.31 trillion and is predicted to reach $2.1 trillion by 2030 (Bommer et al., 2018). In addition to the huge expenditure and impact on the existing medical infrastructure, the cost of treatment and management itself is becoming a major challenge, particularly in low-and middle-income countries (Chow et al., 2018).

People with T2D are prone to micro and macrovascular diseases, peripheral neuropathy, cognitive decline, and depression (van Sloten et al., 2020) and T2D is considered as a significant risk factor for cardiovascular and chronic kidney diseases (Sarwar et al., 2010). T2D can also adversely affect the immune system, making them more susceptible to infections (Joshi et al., 1999; Magliano et al., 2015; Misra et al., 2018) and at increased risk of illness from infectious diseases, such as flu or Covid-19 (Bornstein et al., 2020). Besides being one among the top ten causes of death globally, T2D incidence is rising even in young adults because of unhealthy lifestyle (Lascar et al., 2018; Saeedi et al., 2020).

DNA damage and Repair

DNA or deoxyribonucleic acid is the hereditary material which contains the genetic information that controls all cellular functions in an organism. DNA has a double-helical structure with sugar–phosphate backbones on the outside and base pairs on the inside. It consists of subunits called nucleotides joined by phosphodiester bonds and each nucleotide subunit is composed of three parts: a five-carbon sugar, a phosphate group, and a nitrogenous base (Allison, 2007).

Although DNA is packaged into condensed chromatin structure, as part of transcription or replication they are unwound, nicked, copied, broken, and recombined. Reactive metabolites and oxidation products from the cellular metabolic processes can damage DNA, in addition to radiation and other genotoxins from exogenous sources. Resultant assault on DNA leads to tens of thousands of DNA lesions per day in every human cell (Nam & Cortez, 2013).

DNA damages can happen because of variety of reasons and the elaborate and complex network of repair mechanism consists of sensors, signals, mediators and effectors that will act in tandem in order to repair the damage or arrest the cell cycle or place the cell in senescent mode or self-destruct the cell (apoptosis), depending upon the nature and intensity of the damage as shown in Fig 1. (Zhou& Elledge, 2000).

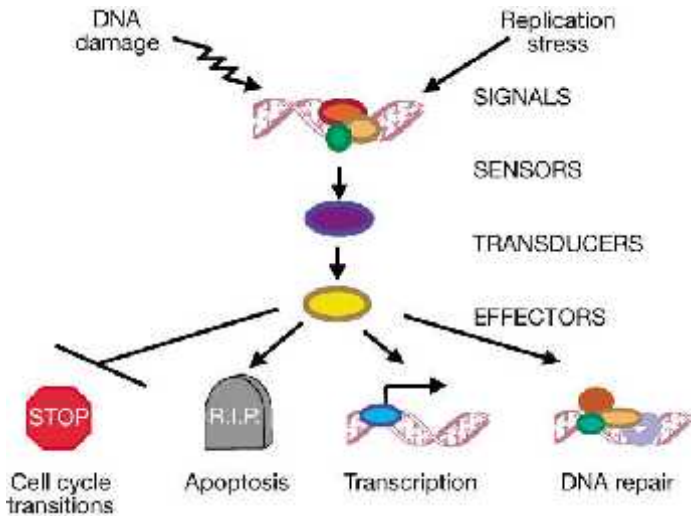

Fig 1. Cellular responses to DNA damage

There are several DNA repair mechanisms that have naturally evolved to tackle different types of damages with different approaches, effectively reversing the damage and maintaining genome integrity. The various factors that could damage the DNA, the resultant type of damage and the corresponding repair mechanism that operates to correct the damage are summarized below(Sirbu & Cortez, 2013).

Damaging agents	Resultant damage	Repair mechanism
Reactive Oxygen Species (ROS), X-Rays, alkylating agents, Spontaneous errors	8-oxo guanine, Single strand break, Deaminated bases	Base Excision repair (BER)
Replication error	A-G / T-C mismatch, Insertion, Deletion	Mismatch Repair (MMR)
UV light, Polycyclic aromatic hydrocarbons	Bulky DNA lesions, DNA-protein adducts	Nucleotide Excision Repair (NER)
X-rays, ionizing radiations, antitumor agents	Double strand breaks, Inter-strand crosslinks	Non-homologous end joining (NHEJ), Homologous recombination (HR)

T2D and oxidative stress

Type-2diabetes is also associated with oxidative stress (OS). OS refers to the imbalance between the generation of reactive oxygen species (ROS) and their scavenging by the inherent antioxidant defences of the cell (Nikooyeh & Neyestani, 2016; Schieber & Chandel, 2014). The abnormal accumulation of ROS is the underlying pathology in a variety of micro and macrovascular diseases (Bigagli & Lodovici, 2019; Martinet et al., 2002; Shah et al., 2018), endothelial dysfunction, atherosclerotic plaques, and subsequent development of cardiovascular diseases and stroke (Bigagli & Lodovici, 2019; Kroese & Scheffer, 2014).

Oxidative DNA damage and repair

One of the most common targets of ROS is the DNA, the biomolecule carrying genetic information, which is fundamental for the functioning and survival of all living organisms.

On average, each human cell experiences more than 10,000 DNA lesions per day (Lindahl & Barnes, 2000), which are typically caused by normal cellular processes. Most of these damages are repaired by the organism's inherent repair mechanisms (Li et al., 2016). But any prolonged inability to repair the damages becomes the basis of genomic instability and possible pathological outcomes (Friedberg, 2003; Jackson & Loeb, 2001). At the molecular level, apart from a higher level of OS, T2D condition is also associated with reduced antioxidant capacity, increased oxidative DNA damage (Bigagli & Lodovici, 2019), and impaired DNA damage-repair capability (Shah et al., 2018). Among the DNA nucleobases, guanine is the most oxidized because of its low redox potential (Radak et al., 2019; Shah et al., 2018).

Oxidative stress or excess amount of hydroxyl radicals can turn guanine into 8-hydroxy-2'-deoxyguanosine (8-OHdG). The reaction between the DNA base deoxyguanosine with hydroxyl radical, producing DNA adducts (8-OHdG) is due to the addition of the hydroxyl group at C8 guanine bases (Fig. 2).

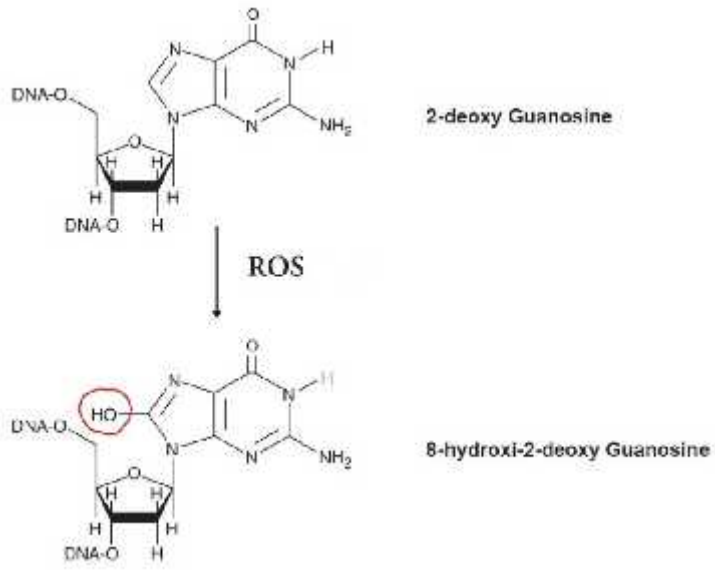

Fig 2.8-OHdG formation due to ROS

In this premise, 8-hydroxy-2'-deoxyguanosine (8-OHdG) is considered as a key biomarker for oxidative DNA damage induced by ROS and is found to be the most prolific oxidative DNA repair product in the human system (di Minno et al., 2016; Kroese & Scheffer, 2014).

Damaged bases in the DNA structure are repaired by Base Excision Repair (BER) mechanisms active in the cell. 8-Oxoguanine glycosylase 1 (OGG1), a short patch gene as part of BER machinery is mainly involved in the repair of oxidatively induced DNA damage (Hoeijmakers, 2009; Odell et al., 2013). Inability or improper repair of oxidative DNA damage can lead to single or double-strand breaks and possibly to mutations, cell senescence, or apoptosis (Shah et al., 2018; Tumurkhuu et al., 2016), which are associated with the etiology and pathophysiology of many diseases including cancer (di Minno et al., 2016; Kroese & Scheffer, 2014; Tumurkhuu et al., 2016).