



**Karolinska  
Institutet**

THE DEPARTMENT OF BIOSCIENCES AND NUTRITION

# **TOXICITY AND BIOCOMPATIBILITY OF NANOPARTICLES, AND STUDIES ON OXIDATIVE STRESS AND DNA DAMAGE**

AKADEMISK AVHANDLING

som för avläggande av medicine doktorexamen vid  
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av

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## ABSTRACT

Oxidative stress is associated with several diseases, either as a cause or a consequence. Chronic kidney disease (CKD) is one example of a disease in which elevated levels of oxidative stress are frequently reported. Oxidative stress, inflammation and malnutrition are risk factors that contribute to an increased risk for cardiovascular disease and a higher morbidity and mortality in CKD patients. In addition, oral complaints such as periodontitis and mouth dryness are recurrently reported. Furthermore, oxidative stress can also be induced by exogenous sources such as toxic agents in our environment. Nanoparticles, which are increasingly used in the society, can potentially cause adverse health effects with oxidative stress as a proposed underlying toxic mechanism. Yet, nanoparticles offer tremendous possibilities for the society, not least within biomedical applications.

The aim of Study I in this thesis was to investigate the effects of kidney disease on DNA damage and oxidative stress in the salivary glands. The comet assay was used for the analysis and the results showed that the DNA damage in predialysis patients (CKD patients not yet on dialysis) was higher compared to controls as well as CKD patients on dialysis. The dialysis patients showed lower levels of DNA damage compared to the controls. There were no differences between the groups regarding the oxidative DNA damage. The inflammation and uremic markers were elevated in all CKD patients compared to the controls. The results suggest that the DNA in salivary glands are affected differently compared to in circulating blood cells that have been studied in previous studies in CKD patients, potentially due to upregulated DNA repair and antioxidative mechanisms in the peripheral tissue.

The aim of Study II was to examine health effects of dietary supplementation with an extract of sea buckthorn rich in antioxidants and fatty acids. The patient group was dialysis patients and the main outcomes were DNA damage and oxidative stress in the salivary glands, as well as saliva production. No significant effects on DNA damage, oxidative DNA damage or saliva production were observed in this crossover intervention study (2 × 8 weeks).

A further aim of the thesis was to investigate the toxicity of nanoparticles *in vitro*. A wide range of nano- and microsized particles was screened for cytotoxicity. Cu- and Zn-based (Cu, CuO, CuZn, Zn, ZnO) nanoparticles were found to be particularly cytotoxic. The Cu-based particles were cytotoxic in a size-dependent manner. Furthermore, the toxicity was found to be dependent on the type of cell investigated.

In Study III the aim was to elucidate the toxic mechanisms of Cu-based (Cu and CuO) nanoparticles. The studies were performed in a leukemic cell line, and the results showed that the Cu nanoparticles were most cytotoxic, followed by CuCl<sub>2</sub> and lastly CuO nanoparticles. The Cu nanoparticles induced high levels of oxidation in an acellular method, as well as slightly increased levels of intracellular reactive oxygen species (ROS) and oxidative DNA damage in the cells. CuO nanoparticles did not induce acellular ROS, and the induction of intracellular ROS and DNA damage was limited. Differences in metal release processes may explain the differences in toxicity modes between Cu and CuO nanoparticles.

In Study IV, the application of nonporous and mesoporous amine-modified silica nanoparticles as plasmid delivery vectors was explored. Both of the silica particles were found to be biocompatible in the human breast carcinoma cell line that was studied. Nonporous particles were more efficient in the delivery of the plasmids. Addition of serum in the cell medium increased the delivery efficiency as well as restricted the toxicity.