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Effects of Nanonickel Administration on Biochemical Parameters in Wistar Rats

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ABSTRACT

Nanomaterial applications are a field which is rapidly growing. Despite the growing use of nickel oxide nanoparticles, there is little knowledge on their toxicological impact. Despite their powerful advantages, many open ended questions about how these nanoparticles can affect the environment and human health. Present study was conducted to know the effects of nanonickel on biochemical parameters in Wistar rat at NOAEL dose for a period of 90 days. Thirty five, six weeks old, Wistar rats of both sexes were divided randomly in two groups viz. group I with 20 rats as control group and group II with 15 rats as treatment group. Group II was orally administered nickel oxide nanoparticles of less than 50 nm diameter in distilled water at NOAEL dose of 5 mg/kg body weight/day and these were gavaged once daily for 90 days. Blood was collected by cardiac puncture from 5 rats from each group at 0 (only from group I), 30th, 60th and 90th DPT and serum was used for biochemical studies. Group I rats revealed no significant change in any biochemical parameter. Group II rats showed a significant increase in serum creatinine, serum aspartate aminotransaminase (AST) and serum alanine aminotransaminase (ALT), significant decrease in total protein and gamma globulin and non significant increase in glucose and globulin values as compared to control group. It can be concluded from the present studies that nanonickel exerted adverse effects on these biochemical parameters in Wistar rats at NOAEL dose administered for a period of 90 days. Our research stated that nickel nano-particles adversely alter rats biochemical profile. Further investigations to address the mechanism are required by what physiological path these nano-nickel display their *in vivo* toxicity.

HIGHLIGHTS

- Effect of nickel nano-particles is well defined on biochemical parameters of Wistar rats.
- Nickel nanoparticle severely effects biochemical profile of laboratory animals.

Keywords: Serum creatinine, Serum glucose, Serum Alanine Transaminase (ALT), Serum Aspartate Transaminase (AST), *In-vivo* toxicity, Wistar rats

Nanoparticles got exceptional attention worldwide due to its numerous applications and adverse effects. It has been estimated that landfills (63%±91%) and soils (8%±28%) receive the largest share of emissions of nanoparticles followed by aquatic environment (7%) and air (1.5%) (Bundschuh *et al*., 2018). In the year 2005, Economic Co-operation and Development (OECD) Concerns regarding human health safety and formed a committee to tackle nanoparticles safety problems (Srivastav *et al*., 2017). The demand of nanoparticles is very fast but it also has some potential health risk (Ema *et al*., 2010). The exponentially increasing demand for nanoparticles in many applications are due to their incredible, exceptional and amazing properties, which make them different from bulk materials

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(Remya *et al*., 2015). Nickel nanoparticles characterised by high reactivity, high magnetism, high surface area, low melting point and low auto ignition temperature. Nickel oxide nanoparticles has about molecular weight of 74.6 gm. Nickel is a silver white coloured metallic chemical element which is present in the earth's crust (Arita *et al*., 2012).

Nickel and its compounds are commonly used in industry due to their sole physical and chemical properties. These are solid, stronger than steel, ferromagnetic and highly resistant to rusting and corrosion. Nickel nanoparticles are frequently used in biological applications like magnetically guided drug delivery systems for many therapeutic purposes (Prijic and Sersa, 2011). Nickel nanoparticles cause increase in serum proteins such as α1-antitrypsin, α2-macroglobulin and ceruloplasmin. Nickel nanoparticle treatment causes significant dose dependent hyperglycaemia, reduction in serum urea and significant increase in urea in the urine of male rats (Weischer *et al*., 1980). In males, exposure to nickel nanoparticles causes increased serum glucose, while in females the serum glucose level decreases (Barceloux, 1999). Amplified levels of glucose in males may be attributed to the improved breakdown of glycogen stores in the tissues (Belanger *et al*., 2011) as well as due to the formation of glucose by gluconeogenesis (Shaikh and Desai, 2016). While forced feeding or chronic nickel nanoparticle exposure leads to decrease in serum glucose level (American Biogenics Corporation, 1988). Reduction in total protein concentration is due to incomplete protein synthesis in the liver, inadequate intestinal absorption, and loss of protein due to inadequate renal function (Johnson *et al*, 1999). The reduced levels of total protein and albumin may be attributed to the ability of nanonickel to induce significant damages at gene level, by the damage caused by reactive oxygen species (ROS) to DNA structures (Ali and Mohamed, 2019). In addition, the reduction in protein levels can be attributed to the leakage of albumin and amino acids from the renal tubules as a result of kidney dysfunction (Saad *et al*., 2016). It may be assumed that inhalation of nickel in low doses does not show significant cardiovascular abnormalities. But a moderate level to high level dose may induce pathophysiological changes relevant to atherogenic events, including increased oxidative stress, inflammatory response and coagulation activity (Alissa and Gordon, 2011). The increased accumulation of nanonickel content in kidney tissues may be ascribed to the higher metabolic activity of kidney and detoxification of foreign bodies (Nwokocha *et al*., 2011). Exposure of nickel nanoparticle for short period of time causes renal damage and haematuria (Kasprzak *et al*., 1980).

MATERIALS AND METHODS

Biochemical Assays

Blood samples from 5 rats from each group (both groups I and II) were collected at 0, 30th, 60th and 90th DPT. Serum was separated from blood samples and the biochemical parameters viz. total serum protein, serum albumin, serum glucose, serum globulin, serum creatinine, serum aspartate aminotransferase (AST) and serum alanine transaminase (ALT) were studied using commercial kits with trade name Erba.

Total serum protein

In tests and control rats, total serum protein was measured using standard protocol given along with Erba total protein kit.

Serum albumin

In tests and control rats, serum albumin was measured using standard protocol given along with Erba albumin kit.

Serum globulin

Concentration of the serum globulin was measured by subtracting concentration of serum albumin form concentration of serum total protein.

Serum gamma globulin

Serum gamma globulin concentration was measured by mixing ammonium sulphate and sodium chloride solution and serum. After mixing, the solution was kept in ice bath for overnight and then it was centrifuged to separate the precipitate. Precipitate obtained was then dissolved in the NSS and biurate regent will be mixed and optical density was read against 555 nm.

Serum creatinine

In tests and control rats, serum creatinine was determined using standard protocol given along with Erba creatinine kit.

Serum glucose

In tests and control rats, serum glucose was determined using standard protocol given along with Erba glucose kit.

Serum Alanine Transaminase (ALT)

In tests and control rats, serum ALT was determined using standard protocol given along with Erba ALT kit.

Serum Aspartate Transaminase (AST)

In tests and control rats, serum AST was determined using standard protocol given along with Erba AST kit.

RESULTS AND DISCUSSION

Serum glucose

Mean serum glucose values of experimental rats in different time intervals expressed in mg/dl and are presented in Table 1. Mean values for group I rats were 157±11.75, 169±3.67, 163±8.06 and 165±7.76 mg/dl at 0, 30th, 60th and 90th DPT, respectively. In group II rats, these values were 157±11.75, 173±36.47, 176±13.11 and 169±10.75 mg/dl at 0, 30th, 60th and 90th DPT, respectively. There were increase in mean serum glucose value by 2.31%, 7.91% and 2.36% at 30th, 60th and 90th DPT in treated group as compared to control group. There was no significant difference both in control as well as in treated group. When these values were compared with in the same group at different time intervals, there is no significant difference in groups I and I rats.

Table 1: Serum glucose values in (mg/dl) of experimental rats at different time intervals (Mean ± SE)

Day Post Treatment	Serum glucose values in g/dl (Mean ± SE)	
	Group I (Control)	Group II (Treated)
0	157±11.75^{aA}	157±11.75^{aA} (0%)
30	169±3.67^{aA}	173±36.47^{aA} (2.31%)
60	163±8.06^{aA}	176±13.11^{aA} (7.97%)
90	165±7.76^{aA}	169±10.75^{aA} (2.36%)

*Alphabetical letters (A and B) indicate significant (P<0.05) difference between groups at a particular DPT (DPT = Day Post-Treatment) whereas different alphabetical letters (a and b) indicate significant (P<0.05) difference within days in a particular group.

Total serum protein

Mean total serum protein values of experimental rats in different groups at different time intervals, expressed in g/dl and are presented in Table 2. Mean values for group I rats were 5.4±0.49, 6.5±0.132, 5.53±0.53 and 5±0.38 g/dl at 0, 30th, 60th and 90th DPT, respectively. In group II, these values were 5.4±0.49, 5.4±0.44, 5.09±0.31 and 3.9±1.09 g/dl at 0, 30th, 60th and 90th DPT, respectively. There was a decrease in mean total serum protein values by 16.92%, 7.95% and 22% at 30th, 60th and 90th DPT in group II rats as compared to group I rats. There were significant differences in total serum protein values at 30th and 90th DPT in treated rats as compared to control rats. When these values were compared with in the same group at different time intervals, there was significant difference in group II rats at 90th DPT.

Table 2: Total serum protein in (g/dl) of experimental rats at different time intervals (Mean ± SE)

Day Post Treatment	Total serum protein in g/dl (Mean ± SE)	
	Group I (Control)	Group II (Treated)
0	5.4±0.49^{aA}	5.4±0.49^{aA} (0%)
30	6.5±0.132^{aA}	5.4±0.44^{aB} (-16.92%)
60	5.53±0.53^{aA}	5.09±0.31^{aA} (-7.95%)
90	5±0.38^{aA}	3.9±1.09^{bB} (-22%)

*Alphabetical letters (A and B) indicate significant (P<0.05) difference between groups at a particular DPT (DPT = Day Post-Treatment) whereas different alphabetical letters (a and b) indicate significant (P<0.05) difference within days in a particular group.

Serum albumin

Mean serum albumin values of experimental rats in different groups at different time intervals are expressed in g/dl and presented in Table 3.

Table 3: Serum albumin in (g/dl) of experimental rats at different time intervals (Mean ± SE)

Day Post Treatment	Serum albumin in g/dl (Mean ± SE)	
	Group I (Control)	Group II (Treated)
0	2.42±0.18^{aA}	2.42±0.18^{bA} (0%)
30	3.34±0.48^{bA}	1.58±0.4^{bB} (-52.69%)
60	2.73±0.32^{aA}	2.66±0.17^{bA} (-2.56%)
90	2.55±0.18^{aA}	0.8±0.17^{cB} (-68.63%)

*Alphabetical letters (A and B) indicate significant (P<0.05) difference between groups at a particular DPT (DPT = Day Post-Treatment) whereas different alphabetical letters (a, b and c) indicate significant (P<0.05) difference within days in a particular group.

Mean values for group I rats were 2.42±0.18, 3.34±0.48, 2.73±0.32 and 2.55±0.18 g/dl at 0, 30th, 60th and 90th DPT, respectively. In group II rats, these values were 2.42±0.18, 1.58±0.4, 2.66±0.17 and 0.8±0.17 g/dl at 0, 30th, 60th and 90th DPT, respectively. There were decrease in mean serum albumin values by 52.69%, 2.56% and 68.63% at 30th, 60th and 90th DPT, respectively, in group II rats as compared to group I rats. There were significant difference between control and treated rats at 30th and 90th DPT, respectively. When these values were compared with in the same group at different time intervals, there were significant differences in group I rats at 30th DPT and in group II rats at 90th DPT, respectively.

Serum globulin

Mean serum globulin value of experimental rats in both the groups at different time intervals are expressed in g/dl and presented in Table 4. Mean values for group I rats were 2.92±0.5, 2.03±0.22, 2.36±0.2 and 2.55±0.18 g/dl at 0, 30th, 60th and 90th DPT, respectively. In group II rats, these values were 2.92±0.5, 4.9±0.39, 2.7±0.28 and 3.09±1.12 g/dl at 0, 30th, 60th and 90th DPT, respectively. There was increase in mean serum globulin value by 141.37%, 14.41% and 21.18% at 30th, 60th and 90th DPT, respectively, in group II rats as compared to group I rats. There was significant difference between control and treated group at 30th DPT. When these values were compared with in the same group at different time intervals, there was significant difference in group I rats at 30th DPT. There was no significant change in the values of group II rats throughout the period of experimentation.

Table 4: Serum globulin in (g/dl) of experimental rats at different time intervals (Mean ± SE)

Day Post Treatment	Serum globulin in g/dl (Mean ± SE)	
	Group I (Control)	Group II (Treated)
0	$2.92±0.5^{bA}$	$2.92±0.5^{aA}$ (0%)
30	$2.03±0.22^{aB}$	$4.9±0.39^{aA}$ (141.37%)
60	$2.36±0.2^{bA}$	$2.7±0.28^{aA}$ (14.41%)
90	$2.55±0.18^{bA}$	$3.09±1.12^{aA}$ (21.18%)

*Alphabetical letters (A and B) indicate significant (P<0.05) difference between groups at a particular DPT (DPT = Day Post-Treatment) whereas different alphabetical letters (a and b) indicate significant (P<0.05) difference within days in a particular group.

Serum gamma globulin

Mean serum gamma globulin values of experimental rats in both the groups at different time intervals are expressed in g/dl and presented in Table 5. Mean values for group I rats were 0.44±0.02, 0.51±0.04, 0.47±0.04 and 0.41±0.04 g/dl at 0, 30th, 60th and 90th DPT, respectively. In group II rats, the values were 0.44±0.02, 0.35±0.03, 0.40±0.11 and 0.27±0.03 g/dl at 0, 30th, 60th and 90th DPT, respectively. There were decrease in mean serum gamma globulin values by 31.37%, 14.89% and 34.14% at 30th, 60th and 90th DPT, respectively, in group II rats as compared to group I rats. There were significant differences between control and treated rats at 30th, 60th and 90th DPT. When these values were compared with in the same group at different time intervals, there was significant difference in group II rats at 90th DPT only. In group I rats no significant differences were observed throughout the experiment period.

Table 5: Serum gamma globulin in g/dl of experimental rats at different time intervals (Mean ± SE)

Day Post Treatment	Serum gamma globulin in g/dl (Mean ± SE)	
	Group I (Control)	Group II (Treated)
0	$0.44±0.02^{aA}$	$0.44±0.02^{aA}$ (0%)
30	$0.51±0.04^{aA}$	$0.35±0.03^{abB}$ (-31.37%)
60	$0.47±0.04^{aA}$	$0.40±0.11^{abB}$ (-14.89%)
90	$0.41±0.04^{aA}$	$0.27±0.03^{cB}$ (-34.14%)

*Alphabetical letters (A and B) indicate significant (P<0.05) difference between groups at a particular DPT (DPT = Day Post-Treatment) whereas different alphabetical letters (a, b, c and d) indicate significant (P<0.05) difference within days in a particular group.

Serum creatinine

Mean serum creatinine values in experimental rats in both the groups at different time intervals are expressed in mg/dl and presented in Table 6. Mean values in group I rats were 0.52±0.09, 0.27±0.09, 0.35±0.04 and 0.66±0.04 mg/dl at 0, 30th, 60th and 90th DPT, respectively. In group II rats, these values were 0.52±0.09, 0.48±0.24, 0.72±0.37 and 1.18±0.49 mg/dl at 0, 30th, 60th and 90th DPT, respectively. There were increase in mean serum creatinine values by 77.77%, 105.71% and 78.78% at 30th, 60th and 90th DPT

in group II rats as compared to group I rats. There were significant differences in treated rats at 30th, 60th and 90th DPT as compared to control rats. When these values were compared with in the same group at different time intervals, there were significant differences in group I rats at 30th, 60th and 90th DPT and in group Π rats at 60th and 90th DPT.

Table 6: Creatinine in mg/dl of experimental rats at different time intervals of the experimental period (Mean ± SE)

Day Post Treatment	Creatinine in mg/dl (Mean ± SE)	
	Group I (Control)	Group II (Treated)
0	0.52 ± 0.09^{bA}	0.52 ± 0.09^{cA} (0%)
30	0.27 ± 0.09^{cB}	0.48 ± 0.24^{cA} (77.77%)
60	0.35 ± 0.04^{cB}	0.72 ± 0.37^{bA} (105.71%)
90	0.66 ± 0.04^{aB}	1.18 ± 0.49^{aA} (78.78%)

*Alphabetical letters (A and B) indicate significant (P<0.05) difference between groups at a particular DPT (DPT = Day Post-Treatment) whereas different alphabetical letters (a, b and c) indicate significant (P<0.05) difference within days in a particular group.

Serum aspartate aminotransferase (AST)

Mean serum AST values in experimental rats in both the groups at different time intervals are expressed in IU/L and presented in Table 7 at different time intervals.

Table 7: AST in (IU/L) of experimental rats at different time intervals (Mean ± SE)

Day Post Treatment	AST in IU/L (Mean ± SE)	
	Group I (Control)	Group II (Treated)
0	62.9 ± 3.41^{aA}	62.9 ± 3.41^{aA} (0%)
30	55.2 ± 10.53^{aA}	61.17 ± 22.25^{aA} (9.76%)
60	57.69 ± 8.19^{aA}	61.28 ± 29.92^{aA} (6.22%)
90	51.02 ± 2.79^{bB}	65.41 ± 29.23^{aA} (28.20%)

*Alphabetical letters (A and B) indicate significant (P<0.05) difference between groups at a particular DPT (DPT= Day Post-Treatment) whereas different alphabetical letters (a and b) indicate significant (P<0.05) difference within days in a particular group.

Mean AST values of group I rats were 62.9±3.41, 55.2±10.53, 57.69±8.19 and 51.02±2.79 IU/l at 0, 30th, 60th and 90th DPT, respectively. In group II rats these values were 62.9±3.41, 61.17±22.25, 61.28±29.92 and 65.41±29.23 IU/l at 0, 30th, 60th and 90th DPT, respectively. There were increase in mean serum AST values by 9.76%, 6.22% and 28.20% at 30th, 60th and 90th DPT in group II rats as compared to group I rats. There was a significant difference in mean AST values at 90th DPT in treated rats as compared to control rats. When these values were compared with in the same group at different time intervals, there was significant difference in group I rats at 90th DPT only. There was no significant difference in the group II values at any interval throughout the experimental period.

Serum alanine amino transaminase (ALT)

Mean serum ALT values in experimental rats in both the groups at different time intervals are expressed in IU/L and presented in Table 8 at different time intervals. Mean values of group I rats were 58.86±7.26, 53.53±17.80, 42.43±5.03 and 73.9±10.28 IU/l at 0, 30th, 60th and 90th DPT, respectively. In group II rats, these values were 58.86±7.26, 58.86±7.26, 77.08±33.06 and 201±50.19 IU/l at 0, 30th, 60th and 90th DPT, respectively. There were increase in mean serum ALT values by 9.95%, 81.66% and 171.99% at 30th, 60th and 90th DPT in group II rats as compared to group I rats. There were significant differences between control and treated rats at 30th, 60th and 90th DPT. When these values were compared with in the same group at different time intervals, there was no significant difference in group I rats. While In group II rats, there was significant differences at 90th DPT.

Table 8: ALT in (IU/L) of experimental rats at different time intervals (Mean ± SE)

Day Post Treatment	ALT in IU/L (Mean ± SE)	
	Group I (Control)	Group II (Treated)
0	58.86 ± 7.26^{aA}	58.86 ± 7.26^{bA} (0%)
30	53.53 ± 17.80^{aA}	58.86 ± 7.26^{bA} (9.95%)
60	42.43 ± 5.03^{aB}	77.08 ± 33.06^{bA} (81.66%)
90	73.9 ± 10.28^{aA}	201 ± 50.19^{aB} (171.99%)

*Alphabetical letters (A and B) indicate significant (P<0.05) difference between groups at a particular DPT (DPT= Day Post-Treatment) whereas different alphabetical letters (a, b and c) indicate significant (P<0.05) difference within days in a particular group.

In biochemical studies, there was a non-significant increase in serum glucose at all DPT, it may be due the

nickel nanoparticles induced the pathological changes in pancreatic cells resulting in alterations in serum glucose and serum lipids. Similar findings were reported by Weischer *et al*. (1980). Glucose is considered the primary source of energy for cellular activities under stress. In males, exposure to nickel nanoparticles causes increased serum glucose, while in females the serum glucose level decreases (Barceloux, 1999). It may be possible due to the synthesis of excess glucose in treated rats by gluconeogenesis (Shaikh and Desai, 2016). The elevated glucose levels can be due to an increased degradation of the glycogen reserves in the tissues (Belanger *et al*., 2011). Changes in serum glucose levels may indicate an effect on the pancreas, or may be secondary to the marked decrease in body weight gain shown in the study as described by Weischer *et al*. (1980). There was significant decrease in total serum protein in treated rats at 30th and 90th DPT and which might be due to the stress and malabsorption of nutrients from the body. Total serum proteins were reduced in treated groups, which is consistent with the results of Magaye *et al*. (2014). It might also be due to the moderate deficiency in albumin and globulin as well as decrease in serum albumin values. Reduction in total serum protein concentration can occur due to incomplete protein synthesis in the liver, inadequate intestinal absorption and loss of protein due to inadequate renal function (Thomas, 1998). The normal level of total serum proteins results in their synthesis and catabolism in the body. Reduction of total serum protein is associated with a moderate deficiency of globin and albumin, as well as a decrease in total proteins in cases of decreased albumin, which can be seen in severe liver disease (which reduces the synthesis of proteins) and increases catabolism.

There was significant decrease in serum albumin at 30th and 90th DPT, respectively, which might be due to the leakage of albumin from the kidney tubules due to any dysfunction in the kidney or degeneration of kidney tubular epithelium due to the exposure of nanonickel as also evident from the histopathological studies showing damage to glomeruli. Albumin is the major protein in the liver that actually acts as an antioxidant and protects tissues and cells from damage to free radicals. Serum albumin concentration can also be directly affected by renal glomerular damage (Venkatesan *et al*., 2000). Intravenous injection of 1 mg / kg nickel nanoparticle in mice increased albumin levels (Magaye *et al*., 2014). There was significant increase in serum globulin values at 30th DPT, which suggests that the immune system was stimulated by nickel exposure and it might be due to the increase in serum protein like proteins such as α1-antitrypsin, α2-macroglobulin and ceruloplasmin (Das *et al*., 2008). There was a significant decrease in gamma globulin in treated rats as compared to control rats, which may be due to the suppression of immune system of the body by nanonickel. There was a significant increase in serum creatinine in treated rats as compared to control rats. Increase in serum creatinine value occurs in renal problems (Jacobs *et al*., 2004). Creatinine is mainly produced by arginine, glycine and methionine amino acid in the liver. There were significant increase in ALT at 60th and 90th DPT and significant increase in AST at 90th DPT values indicates tissue damage in liver (Yang *et al*., 2008). The increased accumulation of nanonickel content in the liver tissue might be due to the increased metabolic activity of these organs and their function in xenobiotic detoxification (Nwokocha *et al*., 2011).

CONCLUSION

The present study was carried out to investigate serum biochemical alterations in experimental animal model (Wistar rats) on NOAEL dose. At the end of the experimental period, the significant decrease in serum albumin and gamma globulin, while there was significant increase in serum creatinine, hepatic transaminases including Aspartate aminotransferase (AST) and Alanine aminotransferase (ALT) was seen. It was indicating that the Nano nickel severely affects the biochemical parameters of Wistar rats.

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