

Association of nicotinamide adenine dinucleotide content and glucose levels with the oxidative stress in human leukaemia cells

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Abstract

Objectives: This research underscores the pivotal role of NAD in regulating the oxidant/antioxidant system and controlling ROS production in cancer cells. The present study sought to determine whether increasing NAD levels through supplementation can effectively reduce ROS generation in different cell types, including cancer cells.

Methods: HL-60 cells and Raji cell lines were cultured, and HL-60 cells were differentiated into neutrophil-like cells using all-trans retinoic acid (ATRA). Oxidative stress was quantified using the thiobarbituric acid reactive substance (TBARS) assay and NAD. Cells were then challenged with glucose, and the oxidative stress test was repeated. The HL-60 cells are CD38-negative, and the Raji cells are CD38-positive.

Results: NAD levels in HL-60 cells-CD38 negative were significantly ($p=0.001$) higher than ATRA-differentiated cells and RAJI cells. The TBARS levels were significantly ($p<0.05$) higher in cells with lower levels of NAD, particularly in ATRA-differentiated cells, compared to RAJI cells and undifferentiated HL-60 cells. Regarding the incubation of cells with glucose or NAD, cells were incubated with 100 μ M NAD for 24 hours to elevate intracellular NAD⁺ levels. Interestingly, ROS production was significantly reduced in ATRA-differentiated cells, undifferentiated HL-60 cells, and Raji cells after NAD treatment.

Conclusion: Manipulating NAD concentration may indirectly regulate ROS production, potentially offering adjuvant therapeutic advantages in treating diseases associated with oxidative stress, such as cancer.

Keywords: Nicotinamide adenine dinucleotide, Oxidative stress, Antioxidant system, Human leukaemia cells

Plain English Summary

This study sought to investigate whether increasing NAD levels can decrease toxic ROS in cancer cells, with potential clinical applications. To do so, the model was applied to three cell types: HL-60 leukaemia cells, differentiated neutrophil-like cells, and Raji cells. Findings included that low intracellular NAD levels were associated with higher ROS, ATRA-differentiated cells demonstrated low NAD and high oxidative damage, and NAD supplementation reversed these toxic impacts. These findings, with HL-60 cells (101 ± 18), potentially suggest that boosting NAD levels could be a therapeutic approach for diseases associated with oxidative stress, and that CD38 expression correlates with NAD depletion.

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Introduction

Oxidative stress occurs when there is an overabundance of reactive oxygen species (ROS), due to a disproportion between ROS generation and antioxidant defences (1). Both endogenous factors (like increased oxygen levels and inflammation) and exogenous factors (like nutrition, environmental pollution, and smoking) can contribute to elevated ROS production (2, 3, 4). This imbalance may result in cellular damage (5, 6). High levels of oxidative stress have been implicated in various diseases, such as cancer (7, 8). The antioxidant defence system, comprising enzymatic and non-enzymatic antioxidants, plays a crucial role in neutralising the harmful effects of ROS (9). However, high doses of antioxidant nutrients can act as pro-oxidants, potentially increasing oxidative stress (10, 11).

Recent findings recommend a connection between nicotinamide adenine dinucleotide (NAD) and chronic oxidative stress. NAD exhibits a critical role in oxidative stress, energy metabolism, immune activation, cell viability, and other diseases (12, 13). Additionally, NAD is involved in glycolysis regulation (14). The NAD⁺/NADH ratio is crucial for regulating the intracellular redox state, which in turn affects ROS production (15). Aerobic respiration produces more ROS when the NAD⁺/NADH ratio is reduced (16). NAD also influences cellular antioxidant capacity through its phosphorylated form, NADPH, which has several cell-protective functions (17).

NAD⁺ is a fundamental biomolecule and acts as a substrate for several NAD-degrading enzymes, such as CD38, sirtuins, and poly (ADP-ribose) polymerases (PARPs) (18). It is hypothesised that NAD-consuming enzymes like PARP can trigger the cell to produce NAD⁺ through either the de novo or the salvage pathway to protect cellular viability against oxidative stress (19). Intracellular NAD⁺ levels are critical for maintaining cellular vitality against chronic oxidative damage. This is achieved through mechanisms such as promoting oxidative phosphorylation, PARP activation, and sirtuin activation (12). Although NAD's role in redox regulation is known, few studies have quantified its direct effect on oxidative stress in leukaemia cells.

Methods

Cell culture

RPMLI-1640 medium (Sigma, UK) in combination with 10% heat-inactivated fetal calf serum (FCS) (Lonza, UK), penicillin, streptomycin (Lonza, UK), and (2 mM) L-glutamine (Lonza) was used for culturing HL-60 and Raji cell lines, passage 17 and 20, respectively. The cells were maintained in a

humidified incubator at 37°C with 5% CO₂. HL-60 cells (0.2 × 10⁶/ml) were differentiated into neutrophil-like cells using 1 μM all-trans retinoic acid (ATRA) (ATRA; Sigma, UK) (20).

Thiobarbituric Acid Reactive Substance (TBARS) Assay

In this assay, TBARS levels, expressed as malondialdehyde (MDA) equivalents, were measured at 532 nm (21) in both cell lysate and cell culture medium. The MDA levels were determined using a modified Ohkawa method (22). Pellets of cells (5-10×10⁶ cells) were resuspended in 200 μL PBS that was sonicated for 15 seconds. Afterwards, 10% TCA was added and centrifugation of the mixture was carried out at 4°C for 5 min. An equal volume of thiobarbituric acid (4.6 mM) was then added to the supernatant. The reaction mixture was heated at 100°C for 30 minutes, and absorbance measurement was carried out at 532 nm.

Determination of the effects of NAD supplementation on ROS production

HL-60 cells (treated with ATRA or untreated) and RAJI cells (0.5 × 10⁶ cells/mL) were incubated at 37 °C, both with and without 100 μM NAD⁺ for 24 hours. After incubation, the cells were analysed for TBARS levels using the previously described method. The used concentration of 100 μM of NAD⁺ was specifically chosen for physiological relevance.

Glucose challenge

HL-60 cells (differentiated for 24 hours) and RAJI cells, as well as untreated cells, were incubated with 100 μM NAD for 24 hours. After incubation, the cells were harvested in fresh medium and then treated with 25 mM glucose for 60 min. The incubated cells (at 37°C) were then collected for analysis of ROS levels using the TBARS assay. The used concentration of 25 mM glucose was specifically chosen to induce a hyperglycaemic condition as an oxidative stress medium.

Determination of intracellular NAD⁺

For the NAD cycling assay, standards of NAD⁺ (5 to 60 μM) or 1.25-5×10⁶ cells/ mL were extracted and prepared for NAD analysis following established protocols (23, 24, 25). Extracted samples were heated for 10 minutes and then centrifuged. Afterwards, 49 μL of the prepared sample (supernatant) was added to a mixture having 98 mM Bicine, 24 mM NaOH, 1.62 mM PES, 0.41 mM MTT, 19.6 μL ethanol, 3.92 mM EDTA, and 400 U/mL yeast ADH. Measurement of

sample absorbance was carried out at 565 nm after 30 minutes of incubation (23).

Statistical analysis

Data is expressed as mean value ± SEM using a histogram with each bar representing replicates of three samples. A GraphPad Prism application (V9, USA) was used for statistical analysis. Two samples were compared using a two-sample t-test, and one-way ANOVA with Tukey’s post hoc used

for three-sample comparisons. When the P value ≤ 0.05, the difference is considered significant.

Results

The results have confirmed that intracellular NAD levels in HL-60 cells-CD38 negative (2568±415) were significantly (p=0.001) higher than in cells expressing higher levels of the CD38 enzyme, including ATRA-differentiated cells for 5 days (573±142) and RAJI cells (1900±142) (Figure 1 A and B, respectively).

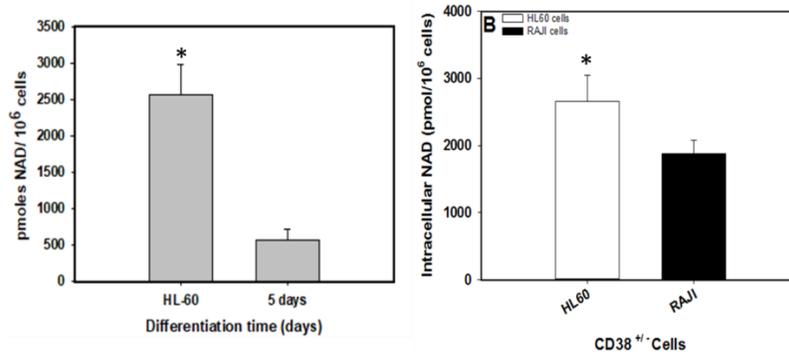


Figure 1: Intracellular content of NAD in (A) HL-60 cells treated with ATRA for 5 days, when compared with control and (B) HL-60 cells compared with RAJI cells

Data is expressed as mean value ± SEM with n = 3, * indicates significant differences at p-value less than 0.05 as compared to other groups using two-sample t-tests

The oxidative stress marker represented by measurement of TBARS levels was found to be significantly (p=0.001) elevated in cells with lower

levels of NAD, particularly in ATRA-differentiated cells (159±57) compared to RAJI cells (99±25) and HL-60 (101±18) (Figure 2).

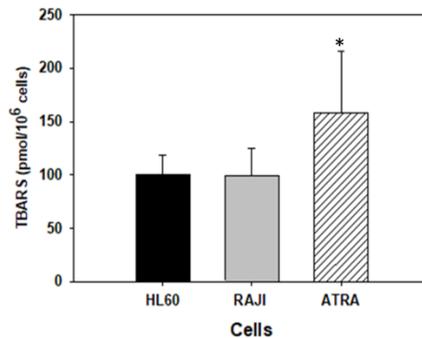


Figure 2: Lipid peroxidation over the time course of (HL-60) differentiation lasts for 5 days when compared with control and Raji cells

Results are expressed as mean ± SEM with n = 3, * indicates significant differences at p-value less than 0.05 as compared to other groups using one-way ANOVA with Tukey's post hoc tests

The lipid peroxidation in all cells was significantly (p=0.001) reduced after incubation with NAD, glucose or a combination of them. The TBARS levels in ATRA-treated cells (159±57) were

significantly (p=0.001) reduced after incubation with NAD (140±25), glucose (84±2) or a combination of them (100±9) (Figure 3).

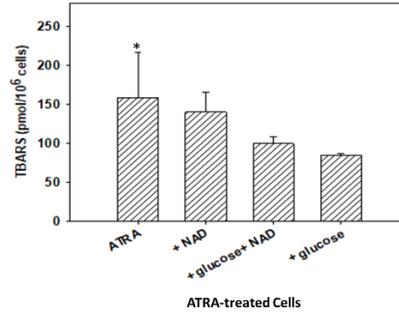


Figure 3: Lipid peroxidation (TBARS levels) after incubation of 1-day-differentiated cells (with or without treatment with 100 μM NAD) for 60 min with (25 mM) glucose, and were compared to control, or with cells incubated with (100 μM) NAD for one day

Results are expressed as mean ± SEM with n = 3, *indicates significant differences at p value less than 0.05 as compared to other groups using one-way ANOVA with Tukey's post hoc tests

The TBARS levels in HL-60 cells (101±18) were significantly (p=0.001) reduced after incubation

with NAD (91±16), glucose (64±1.3) or a combination of them (71±11) (Figure 4).

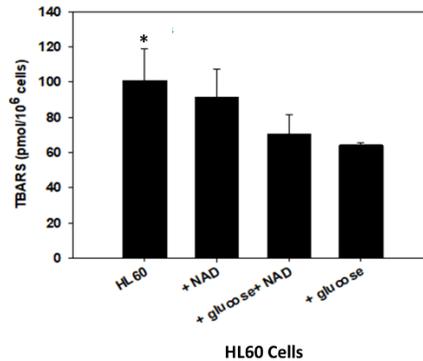


Figure 4: Lipid peroxidation was investigated via TBARS levels after incubation of HL-60 cells (with or without treatment with (100 μM) NAD) for 60 min with (25 mM) glucose, and were compared to control, or with cells incubated with (100 μM) NAD for one day

Results are expressed as mean ± SEM with n = 3, *indicates significant differences at p value less than 0.05 as compared to other groups using one-way ANOVA with Tukey's post hoc tests

Moreover, TBARS levels in RAJI cells (100±25) were significantly (p=0.001) reduced after

incubation with NAD (87±8), glucose (66±0.5) or a combination of them (71±1.4) (Figure 5).

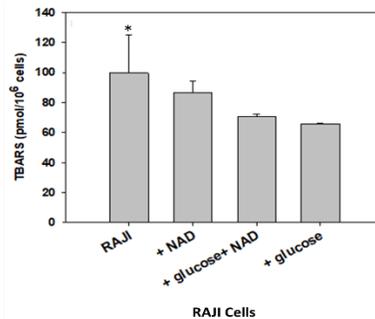


Figure 5: Lipid peroxidation was investigated via TBARS levels after incubation of RAJI cells (with or without treatment with (100 μM) NAD) for 60 min with (25 mM) glucose, and was compared to control, or with cells incubated with (100 μM) NAD for one day

Results are expressed as mean ± SEM with n = 3, *indicates significant differences at p value less than 0.05 as compared to other groups using one-way ANOVA with Tukey's post hoc tests

Discussion

Findings revealed that attenuating ROS production may be linked to NAD levels. This study revealed that NAD⁺ metabolism proves to be the target to regulate reactive oxygen species levels by using extracellular NAD⁺ application. Targeting NAD may play a key role in different diseases linked to oxidative stress (24, 25, 26, 27). These data are consistent with previous reported studies, which explained mitochondrial ROS production (for example, superoxide generation by complex I). This may be through shifting the NAD/ NADH ratio. Importantly, when relative NAD concentration increases, superoxide production decreases (28, 29). Therefore, low ROS production may be related to the direct effect of NAD supplementation. Notably, in cells with low NAD content, adding extracellular NAD may lead to elevated mitochondrial NAD levels compared to NADH levels, resulting in decreased mitochondrial oxygen consumption (aerobic respiration). This may suggest the mechanism responsible for downregulating ROS production. In contrast, using different treatments for upregulating intracellular NAD may cause activation of other members of the sirtuin family with other conceivable beneficial impacts (30).

The previous method for evaluating glycolytic activity and determining glucose's ability to produce lactate under low NAD levels involved the use of glucose (23). In our study, cell treatment was carried out for 60 minutes with 25 mM glucose alone, and TBARS levels (as a biomarker of oxidative stress) were assessed. To examine how NAD levels influence cell physiology, TBARS levels were measured. It was hypothesised that a decrease in NAD levels might lead to an increase in ROS levels due to its impact on the intracellular oxidant/antioxidant balance. The findings illustrated that HL-60 cells (treatment was done with ATRA), untreated HL-60 cells, and RAJI cells all showed a remarkable drop in TBARS levels compared with the control. These results suggest that not only does the intracellular content of NAD affect the oxidant/antioxidant balance, but glucose application may also have a positive effect on cell metabolism even when the intracellular content of NAD is low.

For investigating the effect of intracellular NAD content on TBARS levels, differentiated cells (1 day), Raji, and HL-60 cells were incubated with 100 mM NAD⁺ for 24 hours (to elevate intracellular NAD levels) before being treated (or not) with glucose. The results revealed that TBARS levels in all CD38⁺ cells (Raji cells and differentiated cells) were slightly lower after NAD⁺ supplementation

compared with untreated cells. A similar decline in TBARS levels was observed in CD38⁻ cells (HL-60 cells) treated with glucose followed by incubation with NAD⁺ for 24 hours, even though these cells showed higher NAD levels compared to CD38⁺ cells. Overall, treatment with either NAD⁺, glucose alone, or NAD⁺ with glucose revealed the impact of NAD content on cell metabolism. This outcome underpins the role of CD38 as a main NAD⁺-consuming enzyme and implies that CD38 expression directly contributes to NAD⁺ depletion in leukaemia cells. The inverse correlation between CD38 expression and intracellular NAD⁺ levels has therapeutic consequences for mitigating oxidative stress and cellular function in leukaemia.

Previous studies revealed that cancerous cells utilise glucose (and glutamine) at a higher rate when compared with non-cancerous cells, often described as being "addicted" to glucose (31). In cancerous cells, glucose application might increase cell uptake of glucose, leading to increased glycolytic activity. The enhancement of glycolytic activity (in this study, by glucose supplementation) may also supply adequate pyruvate, which acts as an antioxidant (32). This explains the low ROS production observed when cells are supplied with glucose to enhance glycolytic activity. Additionally, the enhancement of glycolytic activity might promote NAD synthesis, which is also linked to low ROS production as previously explained.

Finally, it is important to note that a decrease in levels of NAD may result in disturbing the oxidant/antioxidant balance for several reasons. First, the decrease in NAD levels may result in decreased levels of phosphorylated nucleotides (NADP or NADPH), which play a major role in the antioxidant system. Second, the drop in NAD levels has also been shown to have further consequences on NADP-dependent processes (18). Specifically, NAD has been involved in the antioxidant function of both catalase and glutathione (33). Third, low NAD levels may disrupt the major functions of NAD-consuming enzymes, specifically PARP, since low NAD levels are linked to DNA damage and oxidative stress (12). Notably, variations in NAD⁺ levels are linked with different diseases associated with oxidative stress (34, 35, 36). These findings encourage future research direction toward using NAD-boosting compounds (nicotinamide riboside, nicotinamide mononucleotide) as potential future strategies for treatment of certain ailments, including ageing, metabolic disorders, and stress.

Study Limitations

The limitations of the present study include that the study only used in vitro cultured leukaemia cell lines, which cannot mirror the complex in vivo milieu of leukaemia patients. Moreover, the study focused on using only one NAD concentration, reflecting no dose-response relationships. No direct mitochondrial function was measured; perhaps the study cannot create clear mechanistic links between NAD levels and mitochondrial oxidative stress. This study used only one oxidative stress marker (TBARS), which provides a limited view of the redox state. Additional markers such as superoxide, hydrogen peroxide, or antioxidant enzyme activity would strengthen future studies. This study tested only high glucose concentrations, which do not mimic the physiological conditions.

Conclusion

This study highlights the role of NAD in regulating the oxidant/ antioxidant balance, especially in reducing reactive oxygen species (ROS) production within leukaemia cells. By increasing intracellular NAD levels through supplementation, a substantial decrease in oxidative stress, as measured via TBARS levels, was observed across diverse cell types. This suggests that manipulating NAD levels can indirectly regulate ROS production, potentially offering adjuvant therapeutic advantages in diseases associated with oxidative stress, such as cancer HL-60

List of Abbreviations

ROS: reactive oxygen species
NAD: nicotinamide adenine dinucleotide
NADH: reduced nicotinamide adenine dinucleotide
NAD+: oxidised nicotinamide adenine dinucleotide
TBARS: thiobarbituric acid reactive substance
ATRA: all-trans retinoic acid
MDA: Malondialdehyde
PARPs: poly (ADP-ribose) polymerases
MTT: 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
EDTA: ethylenediaminetetraacetic acid
ADH: alcohol dehydrogenase
CD: Cluster of differentiation
PES: Polyethersulfone

Declaration

Ethical approval and consent to participate

Not applicable.

Consent for publication

All the author(s) gave consent for the publication of the work under the Creative Commons Attribution-Non-Commercial 4.0 license.

Availability of data and materials

The data and materials associated with this review will be made available by the corresponding author upon reasonable request.

Conflict of Interest

The authors declare no conflict of interest.

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Author's contributions

Al-AZN: Conceptualisation, study design, supervision, data interpretation, and manuscript drafting.

JNK: Methodology development, laboratory experimentation, data acquisition, and statistical analysis.

HSK: Cell culture and biochemical assays (TBARS, NAD quantification), data validation, and results visualisation.

KZM: Data analysis, literature review, and manuscript editing.

Al-DMN: Project administration, funding acquisition, critical revision of the manuscript for intellectual content, and final approval of the version to be published.

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