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Impact of 8-oxoguanine glycosylase-1 gene polymorphism on viral load suppression among subjects with HIV infection

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ABSTRACT:

— ***Objective:*** The impact of 8-oxoguanine glycosylase-1 gene variation on viral load suppression among Human Immunodeficiency Virus-1 (HIV-1) infected subjects is not uncertain. The aim of this study was to explore the potential impact of 8-oxoguanine glycosylase-1 (*OGG1*) variations on the risk of developing HIV infection and disease progression among HIV-infected subjects in Osogbo, Nigeria.

— ***Patients and Methods:*** This cross-sectional study was conducted among 200 HIV-positive subjects [100 newly diagnosed patients and 100 on Highly Active Anti-Retroviral Therapy (HAART)] attending the outpatient clinic dedicated to People Living with HIV (PLWH) at Osun State University Teaching Hospital, Osogbo, and 100 HIV-negative subjects as controls. A structured questionnaire was used to collect relevant medical and socio-demographic information. A multistage random technique was employed in recruiting subjects for the study. Viral Load was determined by Polymerase Chain Reaction and 8-oxoguanine glycosylase (*OGG1*), *Ser326Ser* (*CC*), *Cys326Cys* (*GG*) and *Ser326Cys* (*CG*) genotypes were determined by Restriction Fragment Length Polymorphism (RFLP) method. Data obtained were analyzed using Student *t*-test, Chi-square, analysis of variance and Pearson's correlation coefficient.

— ***Results:*** *Ser326Ser* genotypes were more frequent in PLWH (RR=1.4, OR=3.3, CI=1.53-7.13), indicating that allelotype C may be associated with a higher risk of HIV infection. *Cys326Cys* and *Cys326Ser* genotypes were less frequent in those with viral load >1,000 copies/mL, suggesting that having genotype *Ser326Ser* (RR= 3.226 OR=4.286 CI=0.828-22.173) may be associated with a higher risk of having viral loads >1,000 copies/mL.

— ***Conclusions:*** Single nucleotide polymorphism of *OGG1* may play a significant role in the individual's susceptibility to HIV infection, response to HAART and disease progression. Knowledge of the genetic mutations at an individual level may be beneficial in personalizing HAART therapies and improving their efficacy, especially in patients who show poor response to treatment.

— ***Keywords:*** *HIV infection, 8-oxoguanine glycosylase-1, Viral load, Suppression, Disease progression.*

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INTRODUCTION

The determination of Human Immunodeficiency Virus type 1 (HIV-1) viral load among infected subjects is crucial in disease management. Viral load is a prognostic marker of disease progression among infected subjects. The achievement of suppressed viral load among infected subjects on anti-retroviral drugs is an indication of effective treatment. The variability in viral load observed among HIV-infected subjects may be influenced by several factors, such as the nature of virus, environmental exposure, and host genetics[1,2].

Viral load is recommended as the easily accessible marker in the monitoring, diagnosis and confirming ART failure[3]. The Global Health Sector Strategy on HIV recommends that 95% of people living with HIV know their HIV status; 95% of people diagnosed with HIV receive anti-retroviral treatment; and that 95% of people living with HIV, who get treatment, achieve viral load suppression[4]. HIV viral load suppression is the most important single indicator of successful antiretroviral therapy[4]. It was noted[5] that antiretroviral treatment has been able to improve the prognosis and quality of life of subjects living with HIV by reducing the rate of disease transmission, progression and mortality. Despite progress in therapeutic control, viral mutations continue to accumulate in the peripheral blood compartment over time, indicating either low level reactivation or replication[6]. Apart from the efforts geared towards increasing HIV testing, treatment of all PLWH, improve health education, making medical supplies available and affordable, not much has been reported in literature about host genetics influencing viral load suppression among PLWH on anti-retroviral therapy in Nigeria.

The DNA damage and repair processes are constantly active on a daily basis. Inherited genomic variations, such as single nucleotide polymorphisms (SNPs), may affect the genetic susceptibility to diseases[7]. Host base excision repair (BER) proteins that repair oxidative damage might enhance HIV infection. These proteins include the oxidative DNA damage glycosylases, 8-oxo-guanine DNA glycosylase (*OGG1*) and MutY homolog (*MYH*), as well as DNA polymerase beta (*Pol beta).* While deletion of oxidative BER genes leads to decreased HIV infection and integration efficiency, the mechanism is not completely clear. Cells normally use base excision repair to fix oxidative damage to DNA caused by reactive molecules formed during energy production and other metabolic processes. However, HIV makes use of the base excision repair pathway when inserting its DNA into the host cell genome[8]. Disrupting the repair pathway prevents the virus from concluding an important step in its life cycle. The human 8-oxoguanine glycosylase 1 (*OGG1*) gene, a key component of base excision repair pathway, consists of eight cysteine residues within its active site and is susceptible to oxidative modification. A functional single nucleotide polymorphism (SNP) exists within the *OGG1* gene, as a result of an amino acid substitution of serine with cysteine at position 326 (*Ser326Cys*) within exon 7. Identifying and managing these factors that may help to achieving viral suppression for 95% of those treated by 2030 is imperative. The aim of this study was to explore the potential impact of 8-oxoguanine glycosylase-1 (*OGG1*) variations on the risk of developing HIV infection and disease progression among HIV-infected subjects.

PATIENTS AND METHODS

This study was conducted at Ladoke Akintola University of Technology Teaching Hospital (LAUTECH) Osogbo, Osun State, Nigeria. The prevalence of HIV in Osun state is 0.9% (NAIIS, 2019).

Sample Size Determination

The sample size was determined using the following sample size determination formula for health studies[9]: $n=Z^2PQ/d^2$

and 1.4% prevalence of HIV infection among Nigerians (Federal Ministry of Health; Nigeria HIV/AIDs Indicator and Impact Survey[10]): n is the required sample size, Z is the critical value, and in a two-tailed test this is equal to 1.96. P is the estimated prevalence of HIV in Nigeria. Q is the probability (equal to 1-P), d is the absolute sampling error that can be tolerated.

$$= \frac{1.96^2 \text{ x } 0.014\ (1\text{-}0.14)}{(0.05)^2}$$

The minimum sample size was 21, but 200 HIV-infected subjects were randomly selected for the study.

Study Design/Population

This cross-sectional study consisted of 200 HIV-positive subjects (100 newly diagnosed and 100 on combination HAART) attending the outpatient clinic dedicated to People Living with HIV (PLWH), and 100 HIV-negative subjects as controls. A structured questionnaire was used to collect relevant medical and sociodemographic information. Multistage random technique was employed in recruiting subject for the research. 144 samples (48 naiive, 51 on HAART and 45 negative controls) were randomly selected for genotyping.

Inclusion and Exclusion Criteria

All HIV-positive male and female subjects newly diagnosed and HAART naiive and those on combination highly active antiretroviral treatment (HAART) were randomly recruited into the study. All subjects with history of dyslipidemia, diabetics, hypertension and drug addiction were excluded from the study.

Ethical Approval

Ethical approval was obtained from Ethical Review Committee of LAUTECH Teaching Hospital, Osogbo (LTH/EC/2020/01/444). All participants gave informed consent to participate in the study.

Sample Collection

About 8 mL of venous blood were collected from cubital fossa into an EDTA vacusera bottle, out of which 1 mL of the blood was mixed with DNA/RNA shield using a Zymo Quick-RNA Miniprep Kit (Zymo Research USA). Blood sample for DNA extraction and RFLP analysis was stored at room temperature until analysis was performed. The blood was centrifuged at 1,200 rpm for 20 minutes to separate the serum from the cells. The sera were stored at -20°C for a maximum of one week before the analysis of viral loads was performed.

OGG1 Ser326Cys Polymorphism[11]

DNA was extracted from whole blood stabilized with DNA/RNA shield using a Zymo Quick-RNA Miniprep Kit (Zymo Research, Irvine, CA, USA), according to the protocol suggested by the manufacturer. Extracted DNA was quantified using the NanoDrop 2000 spectrophotometer (Thermo Scientific, Wilmington, DE, USA); the purity and quantity of the extracted DNA were assessed by measuring the OD values and standardized to 10 ngµl^{-1}.

Polymerase chain reaction (PCR) restriction fragment length polymorphism (RFLP) was used to investigate *OGG1* SNP genotypes (n=144). A 234 bp PCR product was amplified using 6 pmol of primers (Inqaba Biotec, Gauteng, South Africa); *OGG1* forward: Forward: 5'-GGAAGGTGCTTGGGGAAT-3', *OGG1* reverse: 5'-ACTGTCACTAGTCTCACCAG-3'). PCR amplification was carried out in 15 µl reaction volumes in separate PCR tubes. The reaction mixture contained 400 ng genomic DNA (5 µl), 10X PCR Buffer (2 µl), 10 mM dNTP mix (0.37 µl), 25 pmol of each primer, 1.5 U Taq DNA polymerase and DNase RNase Nuclease free water (7.93 µl). The reaction mixture was subjected to 94°C for 5 mins as initial denaturation, followed by 30 cycles at 94°C for 1 min, 55°C for 30 sec and 72°C for 1 min, and a final extension step was carried out at 72°C for 5 mins. The target gene segment was successfully amplified from *OGG1*. The PCR product was then resolved on 1.5% agarose gel after electrophoresis. The amplicons were quantified using Image J (U.S. National institutes of Health, Bethesda, MD, USA).

The PCR amplicon underwent restriction endonuclease digestion to determine the presence of the polymorphic restriction site. The products were digested for 12 h by the *Fnu*4HI restriction enzyme (Thermo Fisher Scientific, Wilmington, DE, USA) into two fragments and the fragments were separated on 2% agarose gel containing ethidium bromide. The three possible genotypes were defined based on the three distinct banding patterns observed through ultraviolet spectrophotometer: only 200 bp fragments were assigned to be *Ser/Ser* (*CC*) genotype, both 100 bp and 200 bp fragments were assigned to be *Ser/Cys* (*CG*) genotype, while only 100 bp fragments were assigned to be *Cys/Cys* (*GG*) genotype. The restriction fragments were electrophoresed on an agarose gel (1.8%, 2 µL GelRed, Fremont, CA, USA) and visualized as mentioned above.

RESULTS

A total of 200 HIV-infected subjects and 100 HIV-negative control subjects were recruited for the study. They consisted of 123 males and 177 females with a mean age of 41.24±7.73 years. One hundred and forty-four samples were used for genotyping. Table 1 shows demographic and clinical characteristics of study participants. There was no significant difference in the age, height, weight, body mass index, diastolic and systolic blood pressures among the three study groups. The most frequently prescribed nucleoside reverse transcriptase inhibitors (NRTI) backbone was lamivudine-zidovudine, used by 53.1% of the subjects. Tenofovir-lamivudine, abacavir-lamivudine and didanosine-lamivudine were used by the remaining subjects.

Table 2 shows the socio-demographic characteristics, blood glucose and lipid profile levels among the study participants stratified based on genetic variation in DNA

Table 1. Socio-demographic characteristics of the study participants.

Parameters	HIV Positive subjects on HAART N=100	HIV Positive HAART Naiive subjects N=100	HIV Negative Control subjects N=100	*p*-value
Systolic (mmHg)	113.70±21.07	113.10±17.51	111.80±13.13	0.736
Diastolic (mmHg)	74.40±13.73	73.10±12.12	73.60±9.48	0.739
Height (m)	1.61± 0.07	1.62±0.09	1.62±0.07	0.130
Weight (Kg)	63.65±11.31	59.84±10.25	61.40±11.41	0.050
BMI (kg/m^2)	23.79±3.86	23.1±4.23	23.64±4.6	0.483

HAART= HIV positive subjects on Anti-retroviral drugs; NAIIVE=HIV positive subjects not on anti-retroviral drugs. Data are presented as Mean ± Standard Deviation (SD).

Table 2. Socio-demographic characteristics, blood glucose and lipid profile parameters among study participants stratified based on genetic variation in DNA repair pathway (*OGG1* SNP).

Parameters	*GG+CG* N= 78	*CC* N=66	T	*p*-value
Systolic (mmHg)	110.79±6.22	66±16.35	0.31	0.580
Diastolic (mmHg)	71.71±15.3	73.3±12.07	0.58	0.446
BMI (kg/m^2)	23.31±4.74	23.54±4.39	0.06	0.802
Glucose (mmol/L)	4.33±1.55	4.8±1.88	0.07	0.788
TC (mmol/L)	3.71±0.88	3.77±0.94	1.25	0.266
TG (mmol/L)	0.59±0.23	0.57±0.20	1.46	0.229
LDL-c (mmol/L)	2.36±0.94	2.57±0.95	0.76	0.386
HDL-c (mmol/L)	1.04±0.29	0.91±0.27	0.28	0.600

GG = Cys326Cys; CG = Cys326Ser; CC = Ser326Ser; BMI – Body Mass Index; TC – Total Cholesterol; TG – Triglyceride; LDL-c = Low Density Lipoprotein; HDL-c = High Density Lipoprotein. Data are presented as Mean ± Standard Deviation (SD).

repair pathway (*OGG1* SNP). There was no significant difference in the mean values of all measured parameters based on genetic variants in DNA repair pathway.

Table 3 shows OGG1 SNP frequency distribution among PLWH and HIV-negative control subjects. Some 45 (57.7%) of PLWH and 33 (42.3%) of HIV-negative control subjects had genotypes Cys326Cys+Ser326Cys, while 54 (81.1%) of PLWH and 12 (18.1%) of HIV-negative control subjects had Ser326Ser genotype. A statistically significant difference was observed when frequencies between the two groups were compared. Ser326Ser genotypes were more frequent in PLWH (RR=1.4, OR=3.3, CI=1.53-7.13), suggesting that having genotype Ser326Ser may be associated with higher risk of HIV infection. The odds of susceptibility to HIV infection were 3.3 times higher among those with genotypes GG+CG than those with CC.

Table 4 shows *OGG1* SNP frequency distribution among PLWH on HAART, NAIIVE and negative controls. Some 25.6% of those on HAART, 32.1% of newly diagnosed HIV-positive subjects and 42.3% of HIV-negative control subjects showed genotypes *GG+GC*, while 47.0% of those on HAART, 34.8% of newly diagnosed clients and 18.2% of negative control groups ad genotype CC. The difference was statistically significant when the groups were compared using Chi-square.

Table 5 shows *OGG1* SNP frequency distribution stratified based on HIV RNA viral loads among those on HAART. Some 21 (53.8%) of PLWH with genotypes *Ser326Ser* had their viral load suppressed compared with only 18 (46.2%) among those with genotype *Cys326Cys* and *Ser326Cys*. Also, 12 (83.3%) of PLWH on HAART with genotypes *Ser326Ser* had their viral load not suppressed compared with only 2 (16.7%) percent among those with genotypes *Cys326Cys* and *Cys326Ser*.

Cys326Cys and *Cys326Ser* genotypes were less frequent in those on HAART with viral load ≥1,000, suggesting that having genotype *Ser326Ser* (RR=3.2, OR=4.3, CI=0.83-22.17) may be associated with higher risk of having viral loads ≥1,000 copies /mL.

Table 3. OGG1 SNP frequency distribution among HIV Positive subjects (those on HAART and NAIIVE) and controls.

Frequency	HIV-Positive	HIV-Negative	Total	RR	OR (95% CI)
CC	54 (81.8%)	12 (18.2%)	66 (100%)	1.4	3.3 (1.53-7.13)
GG+CG	45 (57.7%)	33 (42.3%)	78 (100%)		
Total	99 (100)	45 (100)	144 (100)		

GG+CG = Cys326Cys+Ser326Cys, CC = Ser326Ser, RR = Risk Ratio, OR = Odds Ratio, n = sample size.

Table 4. *OGG1* SNP frequency distribution among PLWH on HAART, NAIIVE and negative controls.

Subjects	*(GG+CG)* n (%)	*CC* n (%)	Total n (%)	Chi-square	*p*-value
HAART	20 (25.6%)	31 (47.0%)	51 (35.4%)	12.691	0.002*
Naiive	25 (32.1%)	23 (34.8%)	48 (34.8%)		
Controls	33 (42.3%)	12 (18.2%)	45 (31.3%)		
Total	78 (100.0%)	66 (100.0%)	144 (100%)		

GG+CG = Cys326Cys+Ser326Cys, CC = Ser326Ser. *Statistical significance at 0.01.

Table 5. *OGG1* SNP frequency distribution stratified based on HIV RNA viral loads among those on HAART.

OGG1	Viral load n (%)		Total	RR	OR (95% CI)
	>1,000 copies/mL	<1,000 copies/mL			
CC	10 (83.3%)	21 (53.8%)	31 (100.0%)	3.2	4.3 (0.828-22.173)
GG+CG	2 (16.7%)	18 (46.2%)	20 (100.0%)		
Total	12 (100%)	39 (100%)	51 (100%)		

This analysis shows that the likelihood of not achieving viral load suppression among PLWH with genotype Ser326Ser was 4.3 times more likely than those with genotype *Cys326Cys* and *Cys326Ser*.

DISCUSSION

Human immunodeficiency virus (HIV) remains a persistent public health concern in sub-Saharan Africa. The World Health Organization reported[12] that about 650,000 patients died due to HIV infection in 2021, and sub-Saharan Africa is the most affected region by the infection in the world. There has been a repeated call for an end to HIV pandemic. In 2014 the joint United Nations on HIV/AIDS (UNAIDS) launched the 90-90-90 targets to diagnose 90% of all HIV-positive persons, providing ART for 90% of those diagnosed and achieving viral suppression for 90% of those treated by 2020. A new goal of 95-95-95 has also been set for 2030[13]. Available evidence[4] indicates that early placement of patients on treatment and achievement of viral load suppression reduces mortality, HIV transmission, and improves quality of life. However, while access to HAART has tremendously improved, virologic failure (when antiretrovial therapy fails to suppress and sustain an infected person's viral load to lower than 1,000 copies/mL) remains a common problem. Some authors[14] have suggested that several factors might be associated with virologic failures. Other authors[15] have highlighted several factors believed to be associated with viral suppression –WHO clinical staging 4, suboptimal adherence, poor tolerability, and drug-resistance. SNP polymorphism of proteins may also be involved in the failure of HAART to suppress viral load. However, there is limited information in literature on the impact of genetic variation in DNA repair pathway on viral load suppression.

As HIV progresses, host immunity is depleted, antiretroviral is therefore needed to prevent viral multiplication and slow down the rate of progression. Some authors[16] have reported high rate of virologic failures and investigations[14,15] have been conducted to develop more effective therapies to inhibit HIV replication. Interestingly, studies[1] on host/pathogen interactions have contributed to improved knowledge on HIV molecular pathogenicity in human. Consequently, more investigations[17] have focused on understanding host genetic factors that could potentially modulate cellular susceptibility to HIV replication.

Genetic susceptibility has been suggested[2] as an important determinant of an individual's response to toxic insult. Also, depleted antioxidant levels in patients with HIV infection have been reported[18,19]. An important pathophysiologic consequence of decrease in antioxidant levels is endogenous DNA damage, and the base excision repair pathway might be the most important mechanism to withstand such deleterious effects. The human 8-oxoguanine glycosylase 1 (*OGG1*) gene, a key component of base excision repair pathway, consists of eight cysteine residues within its active site and is susceptible to oxidative modification. This study was designed to investigate the association between *OGG1* polymorphism among HIV-infected subjects.

Results from this study revealed that the frequency of SNP *Ser326Ser* was higher in HIV-positive subjects than in HIV-negative controls and the difference was statistically significant, indicating a possible association between genetic variation in DNA repair pathway and risk of HIV infection in PLWH. This is in agreement with previous findings[9], where the authors reported a relationship between *OGG1* polymorphism and HIV infection in South Africa. It also corroborated the findings of Yoder et al[20], who reported reduction in rate of replication of HIV as a result of *Ser326Cys* polymorphism in the *OGG1* gene sequences. Consequently, findings from this study also revealed that PLWH carrying *Ser326Ser* (*CC*) genotypes had increased susceptibility to HIV infection. The attention on the *Ser326Cys* polymorphism in the *OGG1* gene sequences and in exploring the relationship between this polymorphism and susceptibility to several diseases is imperative to understanding the pathophysiology of HIV infection. It was suggested[21] that the activity of *OGG1* depends on the *OGG1* gene polymorphisms, and that *OGG1 Cys326* is a weaker polymorph than *OGG1 Ser326* in the ability to repair DNA damage. The DNA in human cells is prone to oxidative damage by various endogenous biochemical processes; nonetheless, exposure to hazardous chemicals and lifestyle factors are important determinants of the extent of oxidative DNA damage. Active oxygen free radicals attack the eighth carbon atom in guanine of DNA molecules and can lead to the production of an oxidative adduct: 8-OHdG, a modification product of oxidative damaged DNA, which can potentially lead to the DNA mutation and induce carcinogenesis[22]. *OGG1* as a DNA repair enzyme can specifically remove 8-OHdG and repair damaged DNA. Thus, the expression of *OGG1* gene polymorphisms may affect the activity of *OGGI*[22].

Also, results from this study showed that there was an association between genetic variation and viral load suppression failure. This may be due to the virus and/or host-genetic factors that could potentially modulate susceptibility to HIV replication. Studies[17] have shown that host genetic factors could confer susceptibility or protection against HIV infection, thus suggesting a protective role of a variation of DC-SIGN promoter and genetic resistance to HIV in serodiscordant couples. Similarly, it was reported[23] that some APOBEC3G variants were associated with HIV infection. The baseline viral load level for failure or therapeutic success is 1,000 copies/mL in accordance with WHO Consolidated Guidelines for the Use of Antiretroviral Drugs for the Treatment and Prevention of HIV infections in 2016[4]. Subjects with viral load test below threshold should be considered as having suppressed viral loads, but subjects with more than 1,000 copies/mL after 12 months of treatment were defined as virologic failures[4]. The proportion of PLWH with viral suppression in this study was relatively high (85%), but falls short of the global target of 95%. In 2014-2015, only 32% of the 36.9 million of PLWH achieved viral load suppression. According to a study[24] conducted in 69 countries in 2016, it was reported that viral load suppression was between 7% and 68%. The lowest achievement rates were reported in low and middle-income countries. In the present study, some 46.2% among PLWH with genotypes GG+GC had their viral load suppressed compared with only 53.8% among those with genotype *CC*, while 16.7% of PLWH with genotype *CG+GG* had their viral load not suppressed, compared with 83.3% with genotype CC. Hence, HIV seems to be more suppressed in those with genotype *CG +GG*. The introduction of vision 95-95-95 by WHO to end HIV/AIDS pandemic by 2030 may be hindered by a lot of factors, especially the lack of adequate data on the last '95'. Available records[25] showed that only 52% have attained suppression in Africa and 47% globally. The observed viral load suppression in this study is higher than 81%, 71% and 41% reported in Botswana, Eswatini and Senegal respectively[26]. People are still being infected with HIV, many of those new infections may be transmitted by people who do not know their HIV status, not on treatment or who had started antiretroviral therapy but had not yet become virally suppressed or had poor adherence to their treatment. In addition to their primary goal of keeping people living with HIV in good health, maintaining an undetectable viral load is an important prevention tool within the combination prevention framework. As important as treatment and primary prevention, systemic changes are required to scale up essential health services for all and to retain people in care for life. Approximately 940,000 people died of AIDS-related illnesses in 2017[25], some of whom may have started antiretroviral therapy but were unable to continue. Many of those deaths occurred among people who did not seek medical attention until they became very ill, and when they did seek medical attention the health system was not unable to respond, owing to staff shortages, poor laboratory services or lack of medicines. Despite the remarkable improvement in antiretroviral supplies, one third of people living with HIV does not start treatment until they are very ill and are considered to have advanced HIV disease[26].

CONCLUSIONS

Data from this study indicated that polymorphisms of the *OGG1* gene may have influenced virological outcomes. It showed that genetic variation in DNA repair pathway may have impacted on HIV infection, and HIV infection seems to be more severe among those with genotype *Ser/Ser* (*CC*) compared with those with genotypes *Cys/Cys* (*GG)+Cys/Ser (GC*). A better knowledge of the genetic background at an individual level may be beneficial in personalizing HAART therapies and improving their efficacy, especially in patients who show poor response following initiation of treatment.

Ethics Approval:
The study was approved by the Ethics Review Committee of LAUTECH Teaching Hospital, Osogbo, Osun State, Nigeria (LTH/EC/2020/01/444).

Conflict of Interest:
None declared.

Informed Consent:
All participants gave informed consent before enrolment in the study.

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Availability of Data and Materials:
Data presented are from a Ph.D thesis.

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